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Éditorial

Un élargissement des obligations vaccinales pour permettre leur suppression : un enjeu de santé publique !

More mandatory vaccines, the first step for suppression of obligation: A public health issue

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Les réticences vis-à-vis des vaccins ont toujours existé. Mais aujourd'hui, c'est dans notre pays, le pays de Louis Pasteur, que les doutes vis-à-vis de la sécurité des vaccins sont les plus importants. Plus de 40 % des personnes interrogées en France pensent que les vaccins ne sont pas sûr, 17 % ne sont pas certains de leur efficacité et 12 % jugent que la vaccination des enfants n'est pas importante [1]. Ces résultats issus d'une étude conduite auprès de 67 pays dans le monde montrent que les français sont, de loin, les plus nombreux à douter des vaccins (« seulement » 17 % des personnes interrogées en Europe et 13 % dans le monde).

Les raisons en sont multiples, souvent complexes mais ce n'est pas le sujet ici. Alors que faire ? Comment regagner la confiance des français vis-à-vis des vaccins ? Vastes questions auxquelles le Comité d'orientation de la concertation citoyenne sur la vaccination, sous la houlette du Pr Alain Fischer, immunologiste de renom, et de Madame Claude Rambaud, co-présidente du Collectif interassociatif sur la santé (CISS) ont tenté de répondre à la demande de la ministre de la Santé.

Ce comité d'orientation, composé d'un panel de personnalités d'horizons divers (philosophe, anthropologue, médecins spécialistes de médecine générale, de pédiatrie, d'infectiologie, de spécialiste du droit. . .) ont auditionné plus de 40 représentants des associations de patients, des professionnels de santé, des industriels, et des experts de la vaccination. Ils se sont appuyés sur les conclusions de 2 jurys (un jury citoyen et un jury de professionnels de santé). Bref, une conférence citoyenne dont les recommandations ne devraient pas être discutées même si les propositions, courageuses et somme toute un peu inattendues, peuvent paraître difficiles à mettre en place et requièrent l'implication de tous les acteurs.

Alors que ces recommandations ont été présentées le 30 novembre, en l'absence, doit on le souligner, de la ministre commanditaire du rapport et du Directeur général de la santé, voilà que chacun donne son avis : pour ou contre l'élargissement de l'obligation, pour ou contre la clause d'exemption, pour ou contre l'élargissement des vaccinateurs, pour ou contre l'obligation de l'utilisation du calendrier vaccinal électronique ?

Bien sûr il serait préférable de pouvoir convaincre nos concitoyens de l'intérêt des vaccins plutôt que les soumettre à une obligation de vaccination. Mais dans l'état actuel, est ce réaliste ? Notons que dans d'autres domaines de la santé, l'obligation a porté ses fruits : port de la ceinture de sécurité, limitation de vitesses, interdiction de fumer dans les lieux publics. . . Alors ne peut-on pas tenter l'expérience et faire confiance à ceux qui ont proposé ces recommandations ? C'est la proposition que soutiennent la très grande majorité des sociétés de santé qui se sont exprimées sur le sujet par la voix d'un communiqué de presse et d'une lettre ouverte aux membres de la Commission des affaires sociales de l'Assemblée Nationale ci-dessous.

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Lettre ouverte aux membres de la Commission des affaires sociales de l'Assemblée nationale de la République française : à propos des conclusions du Comité d'organisation de la concertation citoyenne sur la vaccination

Le 21 décembre 2016

Mesdames, Messieurs les Députés,

Nous représentons 27 sociétés de sages-femmes, puéricultrices et médecins[1].

Nous attirons votre attention sur les enjeux actuels de la **politique vaccinale française** gravement mise en danger dans notre pays. Elle concerne toute la population, depuis le nouveau-né (800 000 naissances annuelles) jusqu'aux plus âgés.

Nous avons tous une responsabilité face à cette situation et **nous ne pouvons pas** rester les bras croisés. Votre rôle dans la définition et l'application de la politique vaccinale est essentiel. Si nous ne changeons pas notre politique vaccinale, nous serons bientôt le pays d'Europe le plus mal vacciné.

La vaccination représente l'un des plus grands succès de l'histoire de la médecine. Extrapolée à la population française, une étude mesurant l'impact de la vaccination au cours du XX^{e} siècle publiée récemment, permet d'évaluer à 36 000 le nombre de morts évités chaque année en France par la vaccination, auxquels il faut ajouter les maladies et séquelles [2].

Malgré ces données indiscutables sur l'efficacité de la vaccination, la France est le pays où la proportion de la population exprimant des doutes quant à la sécurité des vaccins est de très loin la plus élevée (41 % des français ont des doutes, versus 17 % en Europe et 13 % dans le monde) [1]. Par ailleurs, les résultats d'une étude menée par l'OMS montrent que c'est en France que les messages négatifs vis-à-vis de la vaccination sont les plus nombreux [3]. Cette méfiance de la population française vis à vis de la vaccination s'accompagne d'une couverture vaccinale insuffisante voire en baisse pour certains vaccins pourtant essentiels (méningocoque, rougeole, grippe, HPV).

À la demande de madame la ministre de la Santé, **une concertation citoyenne** coordonnée par le Professeur Alain Fischer[2], immunologiste français de renommée internationale, et Madame Claude Rambaud[3], représentante des usagers de la santé a travaillé pendant plusieurs mois. Le 30 novembre dernier, son Comité d'orientation a présenté ses recommandations qui vont dans le sens d'une politique vaccinale ambitieuse et affirmée[4]. Elles proposent l'élargissement des obligations vaccinales de la petite enfance qui devrait permettre d'abord d'améliorer la couverture vaccinale vis-à-vis des vaccins pour lesquels il n'existe aujourd'hui par d'obligation mais de « simples recommandations » pour permettre, dans un deuxième temps, de supprimer le régime d'obligation vaccinale. Cette proposition s'accompagne de la gratuite des vaccins.

Dans l'attente de la réponse de madame la ministre de la Santé, les sociétés signataires du communiqué de presse[1], et celles qui nous rejoignent tous les jours, se mobilisent pour dire **qu'il est urgent d'appliquer ces recommandations**. L'Académie de pharmacie, des syndicats médicaux, mais aussi des associations de patients soutiennent également ces propositions. L'Académie de médecine dans la séance de 27 octobre 2015 avait fait des recommandations allant dans le même sens.

Mesdames et messieurs les députés, nous comptons sur vous et votre sens de l'intérêt des français pour appuyer la mise en place rapide de ces mesures indispensables. Nous sommes à votre disposition pour en parler devant la Commission des affaires sociales ou de la manière qui vous paraîtra la plus appropriée. Des vies, des maladies, des épidémies sont en jeu.

Nous vous prions de croire à l'assurance de notre très respectueuse considération.

Pour les sociétés :

Odile Launay, Robert Cohen,

François Vié le Sage

[1] Cf. Communiqué de presse mise à jour en fichier joint.

[2] Médecin, professeur d'immunologie pédiatrique et chercheur, Alain Fischer est titulaire de la chaire Médecine expérimentale au Collège de France depuis 2014. Il est aussi membre titulaire de l'Académie des sciences depuis 2002 et de médecine depuis 2011

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[4] http://concertation-vaccination.fr/.

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Autres sociétés ayant pris position pour les recommandations de la concertation citoyenne :

- Académie nationale de pharmacie : conseil du 16 décembre 2016
- CSMF : Confédération des syndicats médicaux français (APM 19/12/2016) AVNIR : Associations VacciNation Immunodéprimés Réalité

Autre société ayant pris position après les recommandations de la concertation citoyenne :

- Syndicat MG France : http://www.mgfrance.org/index.php/presse/communiques/1475-politique-de-vaccination-mg-france-reclame-plus-de-clarte

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Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

Références

[1] Larson HJ, de Figueiredo A, Xiahong Z, Schulz WS, Verger P, Johnston IG, et al. The State of Vaccine Confidence 2016: global insights through a 67-country survey. EBioMedicine 2016;12:295–301, http://dx.doi.org/10.1016/j.ebiom.2016.08.042.

[2] van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. Lancet Infect Dis 2016 [pii:S1473-3099(16)00027-X].

[3] Heidi J, Larson, et al. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. Vaccine 2014;32:2150–9.

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Editorial

Vaccine: Time to tell the truth!

Vaccination : il est temps de dire toute la vérité

A significant proportion of American measles and pertussis patients in the post-elimination era were intentionally unvaccinated [1]. Parents claim non-medical exemptions to school immunization requirements such as religious and spiritual beliefs, or personal belief exemptions for moral or philosophical reasons. Among the numerous other factors influencing vaccine compliance, benefits of the vaccine and confidence in prelicensure studies on safety and efficacy are also critical. Indeed, while vaccines have provided evident benefits, the primary effectiveness of new vaccine programs depends on public acceptance of vaccination [2]. The vaccine history has been creating social issues since the 18th century with variolation detractors [3]. More recently, the hepatitis B immunization programs of 1995 [4,5] and the 2009 influenza A (H1N1) pandemic contributed to increasing the negative attitudes towards vaccination around the world [6]. The excessive media coverage of vaccines' alleged side effects probably overshadows the risk of vaccine preventable infectious diseases. The concept of "vaccine hesitancy" is thus a growing focus of concern given its great potential for harm [7].

Our day-to-day medical practice also leads us to be confronted with vaccinated adult patients who are disappointed to be suffering from preventable infectious diseases – for instance and most frequently influenza (but also measles and pertussis). Consequently, many patients are convinced that physicians and the media are lying or, at least, do not tell the whole truth. What do people hear daily? Vaccine is effective in preventing infection. Medical terms such as "preventing" or "effective" do not merely describe a reduction of the risk, but rather suggest complete protection, complete effectiveness, and even eradication.

Quite obviously, we mass-produce opponents every day because we do not tell the "whole" truth or we lie by omission. It has also been shown that the Internet contributes to this "mass-production" [8]. Truth-telling is central to the communication between patients and physicians; it is related to the doctrines of informed consent and it is also culture-specific [9]. According to Ekman [10], lying is the act of one person intending to mislead another one, deliberately, without prior notification of this purpose, and without having been asked by the target. Obviously, physicians lie to influence their patients to accept vaccination. They are fairly convinced to do what is best for their patients. Telling them that "vaccines work" is not false information, but it is all the same a lie by omission as it overestimates the power of vaccines. Opponents not only question the safety and necessity of recommended vaccines but also their effectiveness. If we do not accurately inform our patients about the real effectiveness of vaccines, precisely telling them that the influenza vaccine reduces the risk of contracting the infection by 50% but not 100%, that the hepatitis B vaccine reduces the risk by 90% at best but not 100%, we do not tell the truth. In oncology, attitudes and practices of truth-telling to cancer patients have shifted substantially in the past few years [11]. Truth not only has an ethical rationale, but might also have effectiveness justification due to the long-term confidence in vaccine products offered to the population.

Nowadays, in our industrialized countries, physicians are seen as being equal partners with their patients, who have a right to access information and to make their own choices [11]. Understanding the dynamic provisional nature of truth and the relational nature of autonomy is complex and requires further investigations in the psychological area of vaccines. Future research could address many aspects of truth-telling practices with compliance to vaccination as endpoint. Telling the whole truth about vaccine effectiveness would also probably be a means to reduce vaccine hesitancy in the mid- or long-term.

Authorship

We are the exclusive contributors to the conception of the work with final approval of the version published. We agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Phadke VK, Bednarczyk RA, Salmon DA, et al. Association between vaccine refusal and vaccine-preventable diseases in the United States. A review of measles and pertussis. JAMA 2016;315:1149–58.

[2] Duclos P, Okwo-Bele JM, Gacic-Dobo M, et al. Global immunization: status, progress, challenges and future. BMC Int Health Hum Rights 2009;S2:1–11.

[3] Kata A. A postmodern Pandora's box: anti-vaccination misinformation on the Internet. Vaccine 2010;28:1709–16.

[4] Mikaeloff Y, Caridade G, Suissa S, et al. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. Neurology 2009;72:873–80.

[5] Gherardi RK, Coquet M, Cherin P, et al. Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. Brain J Neurol 2001;124:1821–31.

[6] Larson HJ, Cooper LZ, Eskola J, et al. Addressing the vaccine confidence gap. Lancet 2011;378:526–35.

[7] Dubé E, Laberge C, Guay M, et al. Vaccine hesitancy: an overview. Hum Vaccin Immunother 2013;9:1763–73.

[8] Stahl JP, Cohen R, Denis F, Gaudelus J, et al. The impact of the web and social networks on vaccination. New challenges and opportunities offered to fight against vaccine hesitancy. Med Mal Infect 2016;46:117–22.

[9] Surbone A. Telling the truth to patients with cancer: what is the truth? Lancet Oncol 2006;7:944–50.

[10] Ekman P. Telling lies: clues to deceit in the market place, politics and marriage. New York, NY: Norton and Company; 2001.

[11] Beauchamp TL, Childress JF. Principles of biomedical ethics. 4th edn New York: Oxford University Press; 1994.

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General review

Update on infections with human herpesviruses 6A, 6B, and 7

Mise au point sur les herpesvirus humains 6A, 6B et 7

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Abstract

Human herpesviruses 6A, 6B, and 7 (HHV-6A, HHV-6B, HHV-7) are genetically related to cytomegalovirus. They belong to the *Roseolovirus* genus and to the Betaherpesvirinae subfamily. They infect T cells, monocytes-macrophages, epithelial cells, and central nervous system cells. These viruses are ubiquitous and are responsible for lifelong chronic infections, most often asymptomatic, in the vast majority of the general adult population. HHV-6B is responsible for exanthema subitum, which is a benign disease of infants. HHV-6A and HHV-6B also cause opportunistic infections in immunocompromised patients: encephalitis, hepatitis, bone marrow suppression, colitis, and pneumonitis. Their etiological role in chronic diseases such as multiple sclerosis, cardiomyopathy, and thyroiditis is still controversial. The pathogenicity of HHV-7 is less clear and seems to be much more restricted. Chromosomal integration of HHV-6A and HHV-6B is transmissible from parents to offspring and observed in about 1% of the general population. This integration raises the question of potential associated diseases and can be a confounding factor for the diagnosis of active infections by both viruses. The diagnosis of HHV-6A, HHV-6B, and HHV-7 infections is rather based on gene amplification (PCR), which allows for the detection and quantification of the viral genome, than on serology, which is mainly indicated in case of primary infection. Ganciclovir, foscarnet, and cidofovir inhibit the replication of HHV-6A, HHV-6B, and HHV-7. Severe infections may thus be treated but these therapeutic indications are still poorly defined.

Keywords: HHV-7; Exanthema subitum; Opportunistic infections; Chromosomal integration; HHV-6

Résumé

Les herpesvirus humains 6A, 6B et 7 (HHV-6A, HHV-6B, HHV-7) sont génétiquement proches du cytomégalovirus. Ils appartiennent au genre des *Roseolovirus* et à la sous-famille des Betaherpesvirinae. Ils infectent les lymphocytes T, mais aussi les monocytes/macrophages, certaines cellules épithéliales et les cellules du système nerveux central. Ces virus sont ubiquistes et provoquent une infection chronique à vie, le plus souvent asymptomatique, chez la quasi-totalité de la population générale adulte. Le HHV-6B est responsable de l'exanthème subit, maladie bénigne du très jeune enfant. Les HHV-6A et HHV-6B sont responsables d'infections opportunistes chez les patients immunodéprimés : encéphalites, hépatites, insuffisances médullaires, colites et pneumopathies. Leur rôle étiologique dans des maladies chroniques comme sclérose en plaques, myocardiopathies ou thyroïdites est encore controversé. La pathogénicité du HHV-7 est moins bien connue et paraît beaucoup plus restreinte. L'intégration chromosomique des HHV-6A et HHV-6B est transmissible de façon héréditaire et concerne environ 1 % de la population générale. Elle pose la question des éventuelles maladies associées et peut être un facteur de confusion pour le diagnostic des infections actives par ces deux virus. Le diagnostic des infections à HHV-6A, HHV-6B et HHV-7 se fonde plus sur la PCR, qui permet la détection et la quantification du génome

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viral, que sur la sérologie, indiquée essentiellement en cas de primo-infection. Le ganciclovir, le foscarnet et le cidofovir inhibent la réplication de ces virus, ce qui permet le traitement des infections graves. Les indications ne sont cependant pas encore bien codifiées.

Mots clés : HHV-7 ; Exanthème subit ; Infections opportunistes ; Intégration chromosomique ; HHV-6

1. Introduction

Human herpesvirus 6A (HHV-6A) was isolated by accident in 1986 from T cell blood cultures performed to look for new retroviruses [1]. Human herpesvirus 6B (HHV-6B) was identified in 1988 under similar circumstances [2,3]. It is however just recently, in 2014, that converging results of phenotypic and genetic studies led to the classification of HHV-6A and HHV-6B as two distinct species among viruses defined as HHV-6 [4]. HHV-7 is genetically related to HHV-6 and was identified in 1990 [5]. These three viruses are very common in the general population worldwide. Just like other human herpesviruses, they persist indefinitely in the infected organ and may lead to reactivations, which are usually asymptomatic or associated with more or less severe clinical syndromes. The variety of clinical presentations, the high prevalence of the infection, and its chronicity make it difficult to precisely determine the pathogenic role of the three viruses. This issue is associated with at least one major medical challenge: diagnosing and treating severe presentations of active HHV-6A and HHV-6B infections, which correspond to primary infections or reactivations and are susceptible to antiviral drugs that proved effective against cytomegalovirus (CMV) – a virus genetically related to HHV-6A, HHV-6B, and HHV-7 [6].

2. Characteristics of the viruses

HHV-6A, HHV-6B, and HHV-7 have an envelope of 160 to 200 nanometers of diameter, and their genome is a double-stranded linear DNA. The genomes of the viruses are respectively 159, 165, and 145 kilo base pair long [7]. These genomes are quite homologous and present with a similar organization despite their different size; all three viruses belong to the *Roseolovirus* genus. They harbor similar repeated sequences at each of their extremities, with patterns similar to those of telomeric repeated sequences of human chromosomes. The three viruses are also genetically homologous to CMV as all four of them belong to the Betaherpesvirinae subfamily. Viral particles (also known as virions) consist, from the outside to the inside, of the envelope carrying viral glycoproteins, the tegument, and the nucleocapsid containing the genomic DNA. The lipid nature of the envelop confers poor resistance to chemical or physical inactivating agents. HHV-6 species can be distinguished from one another thanks to their different characteristics in terms of culture, genome sequence, and antigenicity [4]. These differences are lacking among HHV-7 strains, even though genetic variations have been observed [8].

HHV-6A and HHV-6B infect many cells in vivo: T cells, especially $CD4^+$ T cells, but also $CD8^+$ T cells, monocytes-macrophages, hematopoietic cells of the bone marrow, epithelial cells of the kidney and salivary glands, endothelial cells, microglial cells, oligodendrocytes, and astrocytes. The CD46 molecule is a cellular receptor for HHV-6A, while the CD134 molecule is a cellular receptor for HHV-6B [9,10]. HHV-7 has a selective tropism for $CD4^+$ T cells, and CD4 is a receptor for that virus. However, in vivo, HHV-7 is observed in the skin, salivary glands, and many other organs [11].

Isolation and repeated cultures of both HHV-6 species are performed at the laboratory with peripheral blood mononuclear cells of healthy donors, while adaptation to lymphocytic, glial, oligodendrocytic, and megakaryocytic cell lines or to human embryonic fibroblasts is not a common characteristic of all isolates [12,13]. Isolating HHV-7 is best performed in purified blood $CD4^+$ T cell cultures. HHV-7 culture is, however, difficult as it does not usually trigger any cytopathic effect and adaptation to lymphocytic cell lines varies. The viral stocks obtained always have a low infectious titer. There is currently no known natural animal model of productive infection with these viruses, even though transgenic mice expressing human CD46 have experimentally been infected with HHV-6A via intracerebral injections [14].

3. Pathophysiology of the infection

Following penetration of the virus into the target cells, the genomic DNA migrates to the cell nucleus where key steps of viral replication take place. Viral genes go through three stages to be transcribed and expressed: immediate early genes, early genes, and late genes. The nucleocapsid is ultimately formed and binds to the proteins of the tegument in the nucleus cell before acquiring the envelope in cytoplasmic vacuoles derived from the Golgi apparatus. These vacuoles then release virions into the cellular membrane by exocytosis [12]. This replication cycle corresponds to the lytic (or productive) cycle that leads to the death of host cells and to virus production that will disseminate through the organism at the time of primary infection or during reactivations. Following primary infection, both species of HHV-6 and HHV-7 latently persist in various sites and cells of the organism, especially in monocytes-macrophages [15]. Various hypotheses have been put forward to explain these latency mechanisms; all of these mechanisms might be present among the various cell types: presence of the sole viral genome in its episomal form with a potentially limited expression of some genes, replication cycle blocked at the intermediate stage or replication cycle completed but controlled and compatible with

the prolonged survival of the host cell. From this latent state, a productive cycle may be reactivated and may lead to a new production of infectious viruses in the blood and in other body compartments such as saliva. However, the selective expression of some viral genes may be enough to induce modifications of cell functions, even in the absence of a complete replication cycle as demonstrated in an experimental study [13].

Chromosomal integration of HHV-6A and HHV-6B DNA is a unique phenomenon among human herpesviruses. It is observed in approximately 1% of the general population [16]. It corresponds to the covalent binding of the viral genome to the cell DNA in the telomeric region of a given chromosome. This binding is present in all cells of the organism and the viral genome may be vertically transmitted by germ cells or horizontally transmitted via tissue or organ transplants. Viral reactivation from an integrated genomic form has already been demonstrated [17].

HHV-6 primary infection triggers a specific immune response that can be identified through its humoral and cellular components [7,18,19]. Serum antibodies react to various viral proteins, and some of these proteins seem to be dominant antigens in serological tests. Cellular immune response may be detected with the proliferation of $CD4^+$ and $CD8^+$ T cells following exposure to viral antigens. However, the number of HHV-6-specific T cells circulating in the blood is low and a major cross-reactivity between HHV-6A and HHV-6B epitopes may be observed. These viruses are able to modulate the inflammatory response and the specific immune response by:

- stimulating the synthesis of proinflammatory cytokines;
- reducing the expression of HLA class I antigens at the surface of infected cells;
- producing analogues of chemokines and chemokine receptors.

These phenomena are believed to help the virus actively replicate by escaping from the immune response [13]. Despite this immune response observed as early as the primary infection, reinfection by exogenous viral strains from the same viral species is possible and these strains coexist with homologous viral strains that are already latently present. This could trigger genetic recombination events [20].

4. Epidemiology

The ubiquitous viruses HHV-6A, HHV-6B, and HHV-7 are widely observed in the general population as Humans are the sole natural hosts [12]. They are primarily transmitted through saliva, very early in life. Breastfeeding does not seem to play any role in the transmission of HHV-6A and HHV-6B, but the presence of HHV-7 in breast milk has been demonstrated and suggests a potential route of transmission [21]. The in utero transmission of HHV-6 as a traditional virus is observed in approximately 1% of pregnancies. This figure is similar to that observed with CMV, but it is believed to be often associated with the presence of viral DNA integrated to the mother's chromosomes even though this mechanism is still not clearly understood [22]. The transmission of HHV-6 through organ transplants has also been reported while its transmission via labile blood products has never been observed [23].

HHV-6B primary infection usually occurs in early childhood, between 6 months and 3 years of age. HHV-7 and HHV-6A primary infections occur later on. Thus, anti-HHV-6 antibodies reappear as early as 6 months of age when the mother's antibodies disappear, while HHV-7 seroconversion occurs at a later stage. There is currently no specific serological test for both HHV-6 species; the exact mean age and frequency of HHV-6A primary infection thus remain unknown. The prevalence of HHV-6B and HHV-7 infections is very high, above 90% in the general adult population. The prevalence of HHV-6A infection is probably very high as well, but it has yet to be precisely measured.

5. Associated diseases

5.1. Primary infection

Many HHV-6A, HHV-6B, and HHV-7 primary infections are asymptomatic. HHV-6B primary infection is often associated with exanthema subitum (also known as roseola infantum or sixth disease), a benign acute disease of infants [3,24] (Table 1). This disease is usually observed in infants aged between 6 months and 3 years. It usually consists of two consecutive phases: fever for 3 to 5 days, often associated with seizures, and then a rubella-like rash on the neck and chest observed when temperature drops and lasting for 1 or 2 days. HHV-6B primary infection may be associated with less specific symptoms and, in some cases, more severe ones with isolated fever, infectious respiratory or digestive syndromes, meningoencephalitis, liver impairment, viral-like syndrome with mononuclear cells in blood, and macrophage activation syndrome [25–28]. Some encephalitis cases associated with HHV-6B primary infection have a particularly poor outcome and may lead to the patient's death or to significant neurological sequelae [29,30]. In this context, the role of HHV-6B in the onset of severe pediatric cases of temporal lobe epilepsy is questioned. Symptomatic HHV-6A primary infections are not as well documented as those caused by HHV-6B [31,32]. HHV-6A or HHV-6B primary infection observed in fetuses during pregnancy leads to a congenital infection that never seems to be associated with clear clinical signs at birth, unlike CMV. However, an impact on the child's future neuropsychological development has been described [33].

Clear HHV-7 primary infections are poorly documented, except for a few potential cases of exanthema subitum [34]. Viral-like syndrome with mononuclear cells in blood, seizures, or other neurological impairments have also been associated with HHV-7 in studies lacking statistical power, while the association with pityriasis rosea is still being questioned [35,36].

5.2. Reactivations and chronic infection

HHV-6A and HHV-6B are responsible for opportunistic infections that mainly correspond to reactivations of these viruses from their latent state during immunodeficiency (Table 1). Symptoms and diseases observed include fever with

Table 1
Diseases associated with HHV-6A and HHV-6B infections.
Maladies associées aux infections à HHV-6A et HHV-6B.

Status of viral infection	Proven association	Suggested association to be confirmed
Congenital infection	–	Impairment of neuropsychological development in infants
Postnatal primary infection	Exanthema subitum (roseola infantum or sixth disease) for HHV-6B	Exanthema subitum for HHV-6A
	Fever	Macrophage activation syndrome
	Seizures	Temporal lobe epilepsy
	Mild respiratory and digestive symptoms	
	Thrombocytopenia	
	Viral-like syndrome with mononuclear cells in blood	
	Encephalitis	
	Hepatitis, colitis	
Reactivation	Fever	Temporal lobe epilepsy
	Skin rash	Transplant rejection
	Thrombocytopenia, leukopenia, anemia	Graft-versus-host disease (GVHD)
	Myelosuppression	Thrombotic microangiopathy
	Encephalitis, neurocognitive deficit	
	Hepatitis, colitis, gastroenteritis	
	Retinitis	
	Pneumonitis	
	Drug-induced hypersensitivity syndrome (DRESS)	
Chronic infection	–	Multiple sclerosis
		Hashimoto's thyroiditis
		Myocarditis, chronic cardiomyopathy
		Rapid progression towards AIDS in HIV-infected patients for HHV-6A
Chromosomal integration[a]	–	Increased risk of angina pectoris
		Increased risk of HHV-6 congenital infection

[a] Observed in approximately 1% of the general population.

rash and cytopenia, pneumonitis, hepatitis, and encephalitis in organ transplant recipients, as well as colitis and retinitis in HIV-infected patients [37–39]. The most common presentations are limbic encephalitis, neurocognitive impairment, and delayed engraftment in patients who underwent a hematopoietic stem-cell transplant [40,41]. HHV-6A and HHV-6B reactivations less often lead to severe diseases in solid organ transplant recipients [42]. Besides, CMV is often concomitantly detected with HHV-6A or HHV-6B and raises the question of each virus sole responsibility in the onset of these diseases. HHV-6 reactivation may be associated with acute transplant rejection but it is still difficult to know if the viral reactivation is the cause or consequence of the rejection.

The role of HHV-6A as a cofactor of the human immunodeficiency virus (HIV) in the progression towards AIDS is mainly supported by in vitro experimental findings: joint infection of $CD4^+$ T cells by both viruses, induction of CD4 receptor expression by HHV-6 in $CD8^+$ T cells and natural killer cells (NK cells) that would thus become susceptible to HIV, and HIV gene transactivation by HHV-6 [43]. However, even though HHV-6A and HHV-6B are frequently detected and responsible for opportunistic infections in HIV-infected patients, their aggravating role in the progression towards AIDS has never been formally proven [44].

Drug-induced hypersensitivity syndrome, also known as drug rash with eosinophilia and systemic symptoms (DRESS), is often associated with HHV-6B reactivations, to such an extent that this association is used as a diagnostic criterion for DRESS by Japanese dermatologists [45]. The disease usually occurs after intake of antibiotics or antiepileptic drugs. It may be characterized by fever, skin rash, adenopathy, cytolytic hepatitis, blood hypereosinophilia, and a significant deterioration of the patient's general status. It has been demonstrated that some of these drugs stimulate the in vitro replication of HHV-6B, that could thus be the cause of the disease [46].

The association between both species of HHV-6 and lymphoid tissue tumors has been suggested based on their experimental carcinogenic power on mouse cells and more recently because of their chromosomal integration capacity. In humans, the viral genome has been isolated from tumor tissues of patients presenting with lymphoma and Hodgkin's disease, sometimes as an integrated form to the cellular genome [47,48]. However, findings from a study conducted on healthy control individuals showed that HHV-6A and HHV-6B are also frequently detected in lymphoid tissues in the absence of tumor [49].

The role of HHV-6A and HHV-6B in the occurrence of autoimmune diseases has been discussed in patients presenting with multiple sclerosis and, more recently, with Hashimoto's thyroiditis [50,51]. These viruses are detected in the central nervous system of patients presenting with multiple sclerosis, especially in demyelinated plaques. Serological data also demonstrates a higher antiviral immune response in individuals presenting with multiple sclerosis, but the topic is still the object of much debate. The same goes for the potential etiological role of these viruses in some cardiomyopathies or chronic arteriopathies [52,53]. Although this finding still needs

Table 2
Diagnostic strategies for HHV-6A, HHV-6B, and HHV-7 infections.
Approches diagnostiques des infections à HHV-6A, HHV-6B et HHV-7.

General strategy	Technique	Indications	Comments
Indirect diagnosis	Detection and avidity assays for IgG and IgM by IF or IE	Primary infection diagnosis Seroprevalence studies	Difficult interpretation in case of reactivation and/or immunodeficiency No distinction between HHV-6A and HHV-6B Cross-reactivity with other *Betaherpesvirinae*
Direct diagnosis	Viral isolation in cell culture	Active infection with infectious virus production	Reference method but time-consuming, expensive, and technically demanding Low sensitivity
	Antigen detection	Active infection with viral gene expression	Low sensitivity Limited availability of reference antibodies
	DNA detection by qualitative PCR	Infection with presence of viral genome in tissues or biological fluid	No distinction between latent infection, active infection, and chromosomal integration
	DNA quantification by quantitative PCR	Active infection with viral genome replication (longitudinal follow-up of viral load) Comparison of the viral load in blood and target organs	Need for standardization (international benchmark) Need to precisely define active infection and chromosomal integration thresholds
	Detection of viral transcripts by RT-PCR	Distinction between latent and active infection Reactivation during chromosomal integration	Currently limited sensitivity Need for standardization
	Digital PCR using microdilution	Precise quantification of viral DNA Identification of a chromosomal integration	Limited sensitivity (to be studied)
	DNA sequencing	Molecular epidemiology Antiviral resistance Identification of reinfections or coinfections by different viral strains	Role of NGS to be studied

IF: immunofluorescence; IE: immunoenzymology; PCR: polymerase chain reaction (gene amplification); RT-PCR: reverse transcriptase–polymerase chain reaction (gene amplification following reverse transcription); NGS: next-generation sequencing.

to be confirmed, the chromosomal integration of HHV-6A and HHV-6B could be a risk factor for angina pectoris [54].

The role of HHV-7 in opportunistic infections and some tumors has been mentioned, but available data is still weak. Paradoxically, detecting HHV-7 infection seems to be correlated with better prognosis for HIV infection. One reason might just be the presence of a sufficient number of $CD4^+$ T cells [55].

6. Diagnosis

6.1. Direct diagnosis

Direct diagnosis aims at detecting the viruses responsible for the infections, at characterizing them – and especially at differentiating HHV-6A from HHV-6B – at defining the indication for antiviral treatment, and at monitoring treatment efficacy. Direct diagnosis relies on the direct detection of viruses and viral components (Table 2). This type of diagnosis targets the viral particles that are released in biological fluids and infected cells of these fluids and tissues. Infected cells are crucial in case of HHV-6A, HHV-6B, and HHV-7 infections, which, in vivo, are mostly intracellular viruses [56].

Biological specimens used for diagnostic tests are whole blood (sampled with an anticoagulant) rather than plasma, saliva, other bodily fluids such as cerebrospinal fluid (CSF) or bronchoalveolar lavage specimen, and tissue biopsies. Biological specimens must be adapted to the observed clinical syndromes and to the relevant diagnostic questions.

Virus isolation from cultures of primary lymphocytic cells is the historical reference method [1,5,7]. However, culture techniques lack sensitivity, are time/staff/reagent-consuming, and are associated with risks related to the production of infectious viruses. They are now mainly used for research purposes.

Viral antigens of HHV-6A, HHV-6B, and HHV-7 may be directly detected in infected cells or tissues using the immunofluorescence or immunohistochemistry technique thanks to monoclonal antibodies [57]. This technique is also mainly used for biomedical research purposes as it has a relatively low sensitivity and is limited by the low number of functional antibodies available.

Detecting genomic DNA by gene amplification (PCR) is currently the reference technique; it is accessible, specific, and very sensitive. Quantitative PCR methods, notably real-time PCR, constituted a significant advance as they reduced the risk of

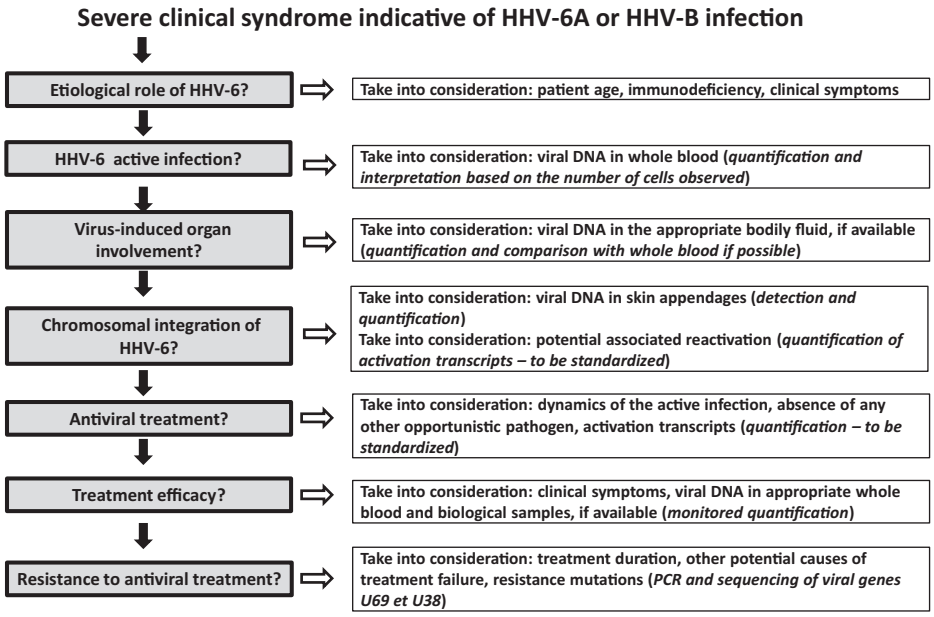

Fig. 1. Decision tree for diagnosing and treating severe HHV-6A or HHV-6B infection. Several of the virological examinations mentioned in this diagram need to be standardized and/or approved for the suggested diagnostic use. The term "HHV-6" refers to both viral species (HHV-6A and HHV-6B).
Schéma décisionnel pour le diagnostic et le traitement d'une infection sévère à HHV-6A ou HHV-6B. Plusieurs des examens virologiques présentés sur ce schéma nécessitent d'être standardisés et/ou approuvés pour l'utilisation diagnostique proposée. Le terme HHV-6 se réfère collectivement aux deux espèces virales HHV-6A et HHV-6B.

contamination by amplified DNA and provided a relatively precise value of the viral load in a given body organ or compartment [58,59]. Detecting and quantifying viral messenger (or transcript) RNA using RT-PCR is an interesting additional strategy to better characterize the active or latent nature of the infection, but this technique needs to be improved [60]. Sequencing viral nucleic acids helps in characterizing them. Among the latest technical innovations of molecular assays, droplet digital PCR helps in quantifying viral DNA without having to use a range of benchmarks. Next-generation sequencing also helps in analyzing the various viral subpopulations within a single specimen [61,62]. All molecular techniques used for the direct diagnosis of HHV-6A, HHV-6B, and HHV-7 infections need to be meticulously standardized using international benchmarks.

6.2. *Indirect diagnosis*

The indirect diagnosis relies on the detection of specific serum antibodies, immunoglobulins G (IgG) and M (IgM), most often using the immunofluorescence technique [63]. Western blot techniques and serum neutralization tests have been described in the diagnosis of HHV-6 infection; they are however mainly used for research purposes. Several factors restrict the use of viral serology, including cross-reactions between HHV-6A, HHV-6B, HHV-7, and CMV antibodies; the absence of a specific serological test able to distinguish HHV-6A infections from HHV-6B infections; the highly frequent HIV-infected status of the general adult population; the absence of correlation between the absolute value or variations of the antibody titer and the presence of an active viral infection; and the alteration of the humoral immune response in some immunocompromised patients. Serological assays are indicated in only two cases: primary infection detected through seroconversion and through the identification of specific IgM, and seroprevalence studies where seropositivity is indicative of a chronic latent infection.

6.3. *Diagnostic strategy and result interpretation*

The diagnosis of HHV-6A, HHV-6B, and HHV-7 infections is usually established based on severe symptoms indicative of primary infection or reactivation. In these situations, priority must be given to the direct diagnostic method [63] (Fig. 1). Indirect diagnosis remains interesting because of its retrospective diagnosis of a primary infection. Otherwise, the identification of a seropositive status is associated with a poor diagnostic impact.

An active infection may be distinguished from a latent one by measuring the DNAemia of HHV-6A and HHV-6B; the threshold in-between those two states is roughly set around 1,000 copies of viral genome per milliliter of whole blood [6]. Successive measures of DNAemia allows for a better assessment of the reactivation curve. As HHV-6A, HHV-6B, and HHV-7 are essentially intracellular viruses, it is quite useful to express the DNAemia in terms of the number of cells present in the circulating blood to avoid underestimating viral replication in case of severe leukopenia [64]. Chromosomal integration of HHV-6A or HHV-6B must be considered in case of a very high and stable DNAemia, reaching or above a million copies of genomic DNA per milliliter of whole blood [13,16]. This chromosomal integration must be confirmed by the presence of HHV-6 DNA in skin appendage specimens (hair follicles, nails), which are devoid of such DNA in the absence of integration, or by the parallel quantification of viral and cellular DNA by digital PCR – method that still needs to be improved. Viral reactivations have, however, been described in patients presenting with chromosomal

integration, and are currently very tricky to identify given the lack of standardized techniques for quantifying viral transcripts [17].

Detecting HHV-6A or HHV-6B DNA in the CSF is highly indicative of an active infection of the central nervous system, especially of encephalopathy. This diagnosis must be considered even if the results of the concomitant DNAemia analysis are not significantly high as reactivation limited to the central nervous system may occur. In case of DNA detection in the CSF, chromosomal integration must be ruled out as it can yet again lead to a false positive result [65]. As for other body compartments susceptible to be the target of HHV-6 active infection, comparing the DNA viral load in tissues and whole blood helps in confirming the presence of in situ viral replication.

The diagnostic strategy and result interpretation would be similar for HHV-7 infections even though the virus pathogenicity is far from being demonstrated; diagnostic strategies are less well developed and used than the ones for HHV-6; and chromosomal integration has so far never been described in this infection.

7. Antiviral treatment

7.1. Available antiviral treatment

In vitro, the replication of HHV-6A, HHV-6B, and HHV-7 is inhibited by foscarnet, ganciclovir, and cidofovir. All these drugs are inhibitors of the viral polymerase DNA encoded by the U38 gene, and are active at concentrations close to those effective against CMV [13]. In contrast, aciclovir and its prodrug (valaciclovir) have no significant activity at the concentrations obtained in treated patients. Ganciclovir and cidofovir need to have gone through three or two phosphorylation steps, respectively, inside the cells to trigger their inhibiting effect, while foscarnet acts directly without any modification required. Phosphorylations are performed by cellular kinases, except for the first step of ganciclovir phosphorylation process, which is catalyzed by a viral phosphotransferase (or protein kinase) encoded by the *U69* gene. This mechanism of action is in line with the localization of the mutations responsible for HHV-6 resistance to antiviral drugs: within the *U69* gene for the resistance to ganciclovir and the *U38* gene for the resistance to the three molecules [66,67]. Note that HHV-6 resistance can appear during the prolonged treatment of CMV infection [66].

7.2. Indications and treatment follow-up

There is no official indication for initiating antiviral treatments targeting HHV-6A and HHV-6B as their effects have only been reported in a few isolated clinical case patients.

However, these treatments may reasonably be proposed as a monotherapy or in combination to patients presenting with severe clinical presentations when one of these viruses is likely to be involved, all the more so in immunocompromised patients (Fig. 1). It is, however, too early to suggest a preventive treatment before diagnosing HHV-6 active infection, or a preemptive treatment for a diagnosed active infection with no associated clinical symptoms. All HHV-6A or HHV-6B active infections do not necessarily progress into severe diseases; some are spontaneously controlled thanks to the immune response. Thus, healthcare professionals seem to agree in saying that limbic encephalitis observed in hematopoietic stem-cell transplant recipients is an indication for curative treatment [13,68].

The clinical and virological efficacy of all antiviral treatments initiated must be monitored, including measuring the viral load using quantitative PCR. The clinical impact of the emergence of resistant viruses is for now quite mild, but resistance must be considered in case of therapeutic failure and must lead healthcare professionals to look for associated mutations using viral genome sequencing techniques.

We stress the need for developing and conducting therapeutic studies with a well-designed method to validate treatments for HHV-6A, HHV-6B, and HHV-7 infections.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Salahuddin SZ, Ablashi DV, Markham PD, Josephs SF, Sturzenegger S, Kaplan M, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science 1986;234:596–601.
[2] Lopez C, Pellett P, Stewart J, Goldsmith C, Sanderlin K, Black J, et al. Characteristics of human herpesvirus-6. J Infect Dis 1988;157:1271–3.
[3] Yamanishi K, Okuno T, Shiraki K, Takahashi M, Kondo T, Asano Y, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. Lancet 1988;1:1065–7.
[4] Ablashi D, Agut H, Alvarez-Lafuente R, Clark DA, Dewhurst S, DiLuca D, et al. Classification of HHV-6A and HHV-6B as distinct viruses. Arch Virol 2014;159:863–70.
[5] Frenkel N, Schirmer EC, Wyatt LS, Katsafanas G, Roffman E, Danovich RM, et al. Isolation of a new herpesvirus from human CD4+ T cells. Proc Natl Acad Sci U S A 1990;87:748–52.
[6] Agut H. Deciphering the clinical impact of acute human herpesvirus 6 (HHV-6) infections. J Clin Virol 2011;52:164–71.
[7] Yamanishi K, Mori Y, Pellett PE. Human Herpesviruses 6 and 7. In: Knipe DM, Howley PM, Cohen JI, Griffin BE, Lamb RA, Martin MA, et al., editors. Fields virology. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2013. p. 2058–79.
[8] Franti M, Aubin JT, Gautheret-Dejean A, Malet I, Cahour A, Huraux JM, et al. Preferential associations of alleles of three distinct genes argue for the existence of two prototype variants of human herpesvirus 7. J Virol 1999;73:9655–8.
[9] Santoro F, Kennedy PE, Locatelli G, Malnati MS, Berger EA, Lusso P. CD46 is a cellular receptor for human herpesvirus 6. Cell 1999;99:817–27.
[10] Tang H, Serada S, Kawabata A, Ota M, Hayashi E, Naka T, et al. CD134 is a cellular receptor specific for human herpesvirus-6B entry. Proc Natl Acad Sci U S A 2013;110:9096–9.
[11] Black JB, Pellett PE. Human herpesvirus 7. Rev Med Virol 1999;9:245–62.
[12] De Bolle L, Naesens L, De Clercq E. Update on human herpesvirus 6 biology, clinical features, and therapy. Clin Microbiol Rev 2005;18:217–45.

[13] Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev 2015;28:313–35.
[14] Reynaud JM, Jegou JF, Welsch JC, Horvat B. Human herpesvirus 6A infection in CD46 transgenic mice: viral persistence in the brain and increased production of proinflammatory chemokines via Toll-like receptor 9. J Virol 2014;88:5421–36.
[15] Kondo K, Kondo T, Okuno T, Takahashi M, Yamanishi K. Latent human herpesvirus 6 infection of human monocytes/macrophages. J Gen Virol 1991;72(Pt 6):1401–8.
[16] Pellett PE, Ablashi DV, Ambros PF, Agut H, Caserta MT, Descamps V, et al. Chromosomally integrated human herpesvirus 6: questions and answers. Rev Med Virol 2012;22:144–55.
[17] Endo A, Watanabe K, Ohye T, Suzuki K, Matsubara T, Shimizu N, et al. Molecular and virological evidence of viral activation from chromosomally integrated human herpesvirus 6A in a patient with X-linked severe combined immunodeficiency. Clin Infect Dis 2014;59:545–8.
[18] Becerra A, Gibson L, Stern LJ, Calvo-Calle JM. Immune response to HHV-6 and implications for immunotherapy. Curr Opin Virol 2014;9C:154–61.
[19] Gerdemann U, Keukens L, Keirnan JM, Katari UL, Nguyen CT, de Pagter AP, et al. Immunotherapeutic strategies to prevent and treat human herpesvirus 6 reactivation after allogeneic stem cell transplantation. Blood 2013;121:207–18.
[20] Achour A, Malet I, Le Gal F, Dehee A, Gautheret-Dejean A, Bonnafous P, et al. Variability of gB and gH genes of human herpesvirus-6 among clinical specimens. J Med Virol 2008;80:1211–21.
[21] Fujisaki H, Tanaka-Taya K, Tanabe H, Hara T, Miyoshi H, Okada S, et al. Detection of human herpesvirus 7 (HHV-7) DNA in breast milk by polymerase chain reaction and prevalence of HHV-7 antibody in breast-fed and bottle-fed children. J Med Virol 1998;56:275–9.
[22] Hall CB, Caserta MT, Schnabel K, Shelley LM, Marino AS, Carnahan JA, et al. Chromosomal integration of human herpesvirus 6 is the major mode of congenital human herpesvirus 6 infection. Pediatrics 2008;122:513–20.
[23] Ward KN, Gray JJ, Efstathiou S. Brief report: primary human herpesvirus 6 infection in a patient following liver transplantation from a seropositive donor. J Med Virol 1989;28:69–72.
[24] Zerr DM, Meier AS, Selke SS, Frenkel LM, Huang ML, Wald A, et al. A population-based study of primary human herpesvirus 6 infection. N Engl J Med 2005;352:768–76.
[25] Asano Y, Yoshikawa T, Suga S, Yazaki T, Kondo K, Yamanishi K. Fatal fulminant hepatitis in an infant with human herpesvirus-6 infection. Lancet 1990;335:862–3.
[26] Asano Y, Yoshikawa T, Kajita Y, Ogura R, Suga S, Yazaki T, et al. Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection. Arch Dis Child 1992;67:1484–5.
[27] Hall CB, Long CE, Schnabel KC, Caserta MT, McIntyre KM, Costanzo MA, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med 1994;331:432–8.
[28] Crawford JR, Kadom N, Santi MR, Mariani B, Lavenstein BL. Human herpesvirus 6 rhombencephalitis in immunocompetent children. J Child Neurol 2007;22:1260–8.
[29] Yoshikawa T, Ohashi M, Miyake F, Fujita A, Usui C, Sugata K, et al. Exanthem subitum-associated encephalitis: nationwide survey in Japan. Pediatr Neurol 2009;41:353–8.
[30] Tesini BL, Epstein LG, Caserta MT. Clinical impact of primary infection with roseoloviruses. Curr Opin Virol 2014;9C:91–6.
[31] Bates M, Monze M, Bima H, Kapambwe M, Clark D, Kasolo FC, et al. Predominant human herpesvirus 6 variant A infant infections in an HIV-1 endemic region of Sub-Saharan Africa. J Med Virol 2009;81:779–89.
[32] Tembo J, Kabwe M, Chilukutu L, Chilufya M, Mwaanza N, Chabala C, et al. Prevalence and risk factors for betaherpesvirus DNAemia in children > 3 weeks and < 2 years of age admitted to a large referral hospital in Sub-Saharan Africa. Clin Infect Dis 2015;60:423–31.
[33] Caserta MT, Hall CB, Canfield RL, Davidson P, Lofthus G, Schnabel K, et al. Early developmental outcomes of children with congenital HHV-6 infection. Pediatrics 2014;134:1111–8.
[34] Tanaka K, Kondo T, Torigoe S, Okada S, Mukai T, Yamanishi K. Human herpesvirus 7: another causal agent for roseola (exanthem subitum). J Pediatr 1994;125:1–5.
[35] Ward KN, Andrews NJ, Verity CM, Miller E, Ross EM. Human herpesviruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. Arch Dis Child 2005;90:619–23.
[36] Rebora A, Drago F, Broccolo F. Pityriasis rosea and herpesviruses: facts and controversies. Clin Dermatol 2010;28:497–501.
[37] Clark DA, Griffiths PD. Human herpesvirus 6: relevance of infection in the immunocompromised host. Br J Haematol 2003;120:384–95.
[38] Boutolleau D, Fernandez C, Andre E, Imbert-Marcille BM, Milpied N, Agut H, et al. Human herpesvirus (HHV)-6 and HHV-7: two closely related viruses with different infection profiles in stem cell transplantation recipients. J Infect Dis 2003;187:179–86.
[39] Gautheret-Dejean A, Agut H, Nicolas JC, Beaugerie L. Roseolovirus DNA in the colonic mucosa of HIV-seropositive patients with diarrhea. Clin Infect Dis 2003;36:1348–9.
[40] Ogata M. Human herpesvirus 6 in hematological malignancies. J Clin Exp Hematop 2009;49:57–67.
[41] Zerr DM, Fann JR, Breiger D, Boeckh M, Adler AL, Xie H, et al. HHV-6 reactivation and its effect on delirium and cognitive functioning in hematopoietic cell transplantation recipients. Blood 2011;117:5243–9.
[42] Razonable RR. Human herpesviruses 6, 7 and 8 in solid organ transplant recipients. Am J Transplant 2013;13(Suppl. 3):67–77 [quiz -8].
[43] Lusso P, Gallo RC. Human herpesvirus 6 in AIDS. Immunol Today 1995;16:67–71.
[44] Spira TJ, Bozeman LH, Sanderlin KC, Warfield DT, Feorino PM, Holman RC, et al. Lack of correlation between human herpesvirus-6 infection and the course of human immunodeficiency virus infection. J Infect Dis 1990;161:567–70.
[45] Yoshikawa K. HHV-6B and HHV-7 in exanthema subitum and related skin diseases. In: Flamand L, Lautenschlager I, Krueger G, Ablashi D, editors. Human herpesviruses HHV-6A, HHV-6B & HHV-7. 3rd ed. Amsterdam: Elsevier; 2014. p. 153–66.
[46] Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, Beneton N, Jidar K, Barbaud A, et al. Amoxicillin-induced flare in patients with DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on Human Herpesvirus 6 replication in vitro. Eur J Dermatol 2010;20:68–73.
[47] Torelli G, Barozzi P, Marasca R, Cocconcelli P, Merelli E, Ceccherini-Nelli L, et al. Targeted integration of human herpesvirus 6 in the p arm of chromosome 17 of human peripheral blood mononuclear cells in vivo. J Med Virol 1995;46:178–88.
[48] Lacroix A, Jaccard A, Rouzioux C, Piguet C, Petit B, Bordessoule D, et al. HHV-6 and EBV DNA quantitation in lymph nodes of 86 patients with Hodgkin's lymphoma. J Med Virol 2007;79:1349–56.
[49] Fillet AM, Raphael M, Visse B, Audouin J, Poirel L, Agut H, et al. Controlled study of human herpesvirus 6 detection in acquired immunodeficiency syndrome-associated non-Hodgkin's lymphoma. J Med Virol 1995;45:106–12.
[50] Leibovitch EC, Jacobson S. Evidence linking HHV-6 with multiple sclerosis: an update. Curr Opin Virol 2014;9C:127–33.
[51] Caselli E, Zatelli MC, Rizzo R, Benedetti S, Martorelli D, Trasforini G, et al. Virologic and immunologic evidence supporting an association between HHV-6 and Hashimoto's thyroiditis. PLoS Pathog 2012;8:e1002951.
[52] Leveque N, Boulagnon C, Brasselet C, Lesaffre F, Boutolleau D, Metz D, et al. A fatal case of Human Herpesvirus 6 chronic myocarditis in an immunocompetent adult. J Clin Virol 2011;52:142–5.
[53] Takatsuka H, Wakae T, Mori A, Okada M, Fujimori Y, Takemoto Y, et al. Endothelial damage caused by cytomegalovirus and human herpesvirus-6. Bone Marrow Transplant 2003;31:475–9.
[54] Gravel A, Dubuc I, Morissette G, Sedlak RH, Jerome KR, Flamand L. Inherited chromosomally integrated human herpesvirus 6 as a predisposing risk factor for the development of angina pectoris. Proc Natl Acad Sci U S A 2015;112:8058–63.
[55] Boutolleau D, Bonduelle O, Sabard A, Devers L, Agut H, Gautheret-Dejean A. Detection of human herpesvirus 7 DNA in peripheral blood reflects mainly CD4+ cell count in patients infected with HIV. J Med Virol 2005;76:223–8.
[56] Achour A, Boutolleau D, Slim A, Agut H, Gautheret-Dejean A. Human herpesvirus-6 (HHV-6) DNA in plasma reflects the presence of

infected blood cells rather than circulating viral particles. J Clin Virol 2007;38:280–5.
[57] Halme L, Arola J, Hockerstedt K, Lautenschlager I. Human herpesvirus 6 infection of the gastroduodenal mucosa. Clin Infect Dis 2008;46:434–9.
[58] Flamand L, Gravel A, Boutolleau D, Alvarez-Lafuente R, Jacobson S, Malnati MS, et al. Multicenter comparison of PCR assays for detection of human herpesvirus 6 DNA in serum. J Clin Microbiol 2008;46:2700–6.
[59] Fernandez C, Boutolleau D, Manichanh C, Mangeney N, Agut H, Gautheret-Dejean A. Quantitation of HHV-7 genome by real-time polymerase chain reaction assay using MGB probe technology. J Virol Methods 2002;106:11–6.
[60] Ihira M, Enomoto Y, Kawamura Y, Nakai H, Sugata K, Asano Y, et al. Development of quantitative RT-PCR assays for detection of three classes of HHV-6B gene transcripts. J Med Virol 2012;84:1388–95.
[61] Leibovitch EC, Brunetto GS, Caruso B, Fenton K, Ohayon J, Reich DS, et al. Coinfection of human herpesviruses 6A (HHV-6A) and HHV-6B as demonstrated by novel digital droplet PCR assay. PLoS ONE 2014;9:e92328.
[62] Sedlak RH, Cook L, Huang ML, Magaret A, Zerr DM, Boeckh M, et al. Identification of chromosomally integrated human herpesvirus 6 by droplet digital PCR. Clin Chem 2014;60:765–72.
[63] Gautheret-Dejean A, Agut H. Practical diagnostic procedures for HHV-6A, HHV-6B, and HHV-7. In: Flamand L, Lautenschlager I, Krueger G, Ablashi D, editors. Human herpesviruses HHV-6A, HHV-6B & HHV-7. 3rd ed. Amsterdam: Elsevier; 2014. p. 9–34.
[64] Gautheret-Dejean A, Henquell C, Mousnier F, Boutolleau D, Bonnafous P, Dhedin N, et al. Different expression of human herpesvirus-6 (HHV-6) load in whole blood may have a significant impact on the diagnosis of active infection. J Clin Virol 2009;46:33–6.
[65] Ward KN, Leong HN, Thiruchelvam AD, Atkinson CE, Clark DA. Human herpesvirus 6 DNA levels in cerebrospinal fluid due to primary infection differ from those due to chromosomal viral integration and have implications for diagnosis of encephalitis. J Clin Microbiol 2007;45:1298–304.
[66] Manichanh C, Olivier-Aubron C, Lagarde JP, Aubin JT, Bossi P, Gautheret-Dejean A, et al. Selection of the same mutation in the U69 protein kinase gene of human herpesvirus-6 after prolonged exposure to ganciclovir in vitro and in vivo. J Gen Virol 2001;82:2767–76.
[67] Bonnafous P, Naesens L, Petrella S, Gautheret-Dejean A, Boutolleau D, Sougakoff W, et al. Different mutations in the HHV-6 DNA polymerase gene accounting for resistance to foscarnet. Antivir Ther 2007;12:877–88.
[68] Razonable RR. Infections due to human herpesvirus 6 in solid organ transplant recipients. Curr Opin Organ Transplant 2010;15:671–5.

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Original article

Proposal for shorter antibiotic therapies

Propositions pour des antibiothérapies plus courtes

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Abstract

Objectives. – Reducing antibiotic consumption has now become a major public health priority. Reducing treatment duration is one of the means to achieve this objective. Guidelines on the therapeutic management of the most frequent infections recommend ranges of treatment duration in the ratio of one to two. The Recommendation Group of the French Infectious Diseases Society (SPILF) was asked to collect literature data to then recommend the shortest treatment durations possible for various infections.

Methods. – Analysis of the literature focused on guidelines published in French and English, supported by a systematic search on PubMed. Articles dating from one year before the guidelines publication to August 31, 2015 were searched on the website.

Results. – The shortest treatment durations based on the relevant clinical data were suggested for upper and lower respiratory tract infections, central venous catheter-related and uncomplicated primary bacteremia, infective endocarditis, bacterial meningitis, intra-abdominal, urinary tract, upper reproductive tract, bone and joint, skin and soft tissue infections, and febrile neutropenia. Details of analyzed articles were shown in tables.

Conclusion. – This work stresses the need for new well-conducted studies evaluating treatment durations for some common infections. Following the above-mentioned work focusing on existing literature data, the Recommendation Group of the SPILF suggests specific study proposals.

Keywords: Treatment duration; Antibiotic therapy; Short treatment; Antibiotic consumption; Antibiotic stewardship

Résumé

Objectifs. – Réduire les durées des traitements antibiotiques est un des moyens permettant une réduction globale de la consommation d'antibiotiques. Les recommandations, même les plus récentes, proposent très souvent des fourchettes de durées de traitement. Le Groupe

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recommandations de la Société de pathologie infectieuse de langue française (SPILF) a effectué une revue de la littérature, dans le but de faire des propositions de durées de traitements courts dans les infections bactériennes.

Méthodes. – Revue de la littérature, jusqu'au 31 août 2015, des essais randomisés abordant les durées de traitement, des recommandations récentes et de leurs argumentaires.

Résultats. – Des durées de traitement courtes (souvent plus courtes que dans certaines recommandations) peuvent être proposées pour les infections respiratoires hautes et basses, les bactériémies dont celles liées aux cathéters veineux centraux, les endocardites infectieuses, les méningites bactériennes, les infections intra-abdominales, urinaires et génitales, les infections ostéo-articulaires, les infections de la peau et des tissus mous et les neutropénies fébriles. Le détail des articles sur lesquels se basent ces propositions est repris dans des tableaux.

Conclusion. – Ce travail, qui montre la pauvreté de la littérature s'intéressant spécifiquement aux durées de traitements antibiotiques, permet d'identifier les études à réaliser de façon prioritaire dans ce domaine.

Mots clés : Durée de traitement ; Antibiothérapie ; Traitement court ; Consommation d'antibiotiques ; Bon usage

1. Introduction

Guidelines on the therapeutic management of the most frequent infections recommend ranges of treatment duration in the ratio of one to two. These ranges take into consideration the various clinical presentations of a single infection and causative agents.

Reducing antibiotic consumption has now become a major public health priority. Reducing treatment duration is one of the means to achieve this objective.

Shorter treatment duration and reevaluation by a senior physician of treatment durations exceeding seven days are part of the suggestions included in the Program for the prevention of healthcare-associated infections (French acronym PROPIAS) and in the report entitled "All together, let's try and save antibiotics" [1].

For instance, the authors of a recent review of randomized study data on the use of biomarkers and specialized mobile team concluded to the greater benefit of a short treatment in lower respiratory tract infections and did not observe any changes in terms of success, relapse, and mortality [2].

The Recommendation Group of the French Infectious Diseases Society (French acronym SPILF) was asked to collect literature data to then recommend the shortest treatment durations possible for various infections.

2. Method

Topics and methods were defined by the SPILF Recommendation Group during Autumn 2014.

Each chapter was written by two members of the group using a literature analysis. Two other members reviewed each chapter before final approval from all members of the group.

The literature analysis focused on guidelines published in French and English. It was then supported by a systematic search on PubMed. Articles dating from one year before the guidelines publication to August 31, 2015 were searched on the website. We used the following search terms to narrow our search down: "treatment duration", "antibiotic", "short treatment", "long treatment", "short course", "short vs. long", and "reduced duration". In addition to this search, a systematic analysis of treatment durations used in randomized trials evaluating the given infection was performed during the specified period. Results of the analysis of all studies used to draft the present document are available in the appendix.

Findings from our work are presented by topics, with the following information for each section:

- a box summarizing the shortest treatments that may be suggested, for standard clinical situations;
- a summary of data that helped in drafting the guidelines;
- a table presenting the main characteristics of studies that we took into consideration.

3. Upper respiratory tract infections

Suggested treatment durations:

- 5 days:
  - acute otitis media (AOM) in children from 2 years of age, without any relapse nor any otorrhea,
  - adult maxillary sinusitis;
- 6 days:
  - group A streptococcal tonsillitis treated with amoxicillin;
- 10 days:
  - AOM in children aged below 2 years, or recurrent AOM, or AOM associated with otorrhea,
  - pediatric maxillary sinusitis,
  - frontal sinusitis.

Method.– Source: Good Practice Recommendations – Systemic antibiotic therapy in routine practice for the treatment of adult and pediatric upper respiratory tract infections (2011), IDSA Guidelines on sinusitis [3], and literature analysis on PubMed from 2011 to 2015.

Key points:

- upper respiratory tract infections are the most frequent cause of antibiotic prescriptions;
- treatment duration has extensively been studied in ENT infections [4–7];
- many antibiotics were launched in the 1990s (cephalosporins and macrolides). The vaccine industry believed shorter treatments to be a market advantage, associated with a potentially better compliance;
- treatment duration has never been used as the primary criterion in French or American guidelines to recommend an agent in the first-line treatment of a given infection. Criteria such as adaptation to bacterial epidemiology, antibiotic resistance, clinical effectiveness, tolerability, and ecological impact have instead rightly been used to guide this choice [3,8];
- one of the main characteristics of these infections is their high rate of spontaneous recovery, thus questioning the benefit of an antibiotic therapy. Cochrane reviews published on the treatment of AOM, group A streptococcal tonsillitis, or sinusitis all conclude to the limited benefit of the antibiotic therapy [9,10]. However, antibiotics are still indicated in most Western countries in the treatment of AOM, Group A streptococcal tonsillitis, and sinusitis;
- considering this high rate of spontaneous recovery, study findings incur a great risk of being wrongly "non-inferior". However, for group A streptococcal tonsillitis, diagnostic criteria and the primary efficacy endpoint (bacterial eradication) are particularly robust and reproducible. Conversely, for the two other ENT infections (AOM and sinusitis):
  - diagnostic criteria are not as robust as the ones used for group A streptococcal tonsillitis (i.e., mainly based on anamnesis and clinical examination for AOM and on anamnesis alone for sinusitis),
  - recovery criteria are only clinical and are quite random as they are mainly subjective criteria; this implies that double-blind studies should only be taken into consideration [11,12].

This is why treatment duration for group A streptococcal tonsillitis is better defined than for AOM (taking into consideration age, relapse, and otorrhea) and sinusitis (taking into consideration age and anatomical site) (Table 1).

The main characteristics of studies considered in this analysis are presented in Table 2.

4. Lower respiratory tract infections

Suggested treatment durations:

- 5 days:
  - COPD exacerbations,
  - pediatric community-acquired pneumonia;
- 7 days: adult community-acquired pneumonia.

A favorable clinical and/or biological outcome could lead to reducing treatment duration (3–5 days), but literature data is still scarce. Studies are currently ongoing.

Source: Good Practice Recommendations – Systemic antibiotic therapy in routine practice for the treatment of adult lower

Table 1
Treatment duration for upper respiratory tract infections.
Durée de traitement des infections respiratoires hautes.

Upper respiratory tract infection	Recommended agent	Treatment duration	Alternatives	
Group A beta-hemolytic streptococcus tonsillitis	Amoxicillin	6 days [0,0]	Cefpodoxime Cefuroxime Azithromycin	5 days [13,14] 4 days 3 days
AOM < 2 years Or recurrent AOM Or AOM associated with otorrhea	Amoxicillin	10 days	Cefpodoxime or erythromycin/sulfafurazole	10 days
AOM other situations	Amoxicillin	5 days	Cefpodoxime or erythromycin/sulfafurazole	5 days
Maxillary sinusitis Children Adults	Amoxicillin	10 days [0] 10 to 14 days [0] 7 days [0] 5 to 7 days [0]	Cefpodoxime or cefuroxime	10 days [8] 10 to 14 days [3] 7 days [8] 5 to 7 days [3]
Frontal sinusitis	Amoxicillin–clavulanic acid	10 days [0]	Cefpodoxime Cefuroxime	10 days

AOM: acute otitis media.

Table 2
References – upper respiratory tract infections.
Bibliographie – infections respiratoires hautes.

Reference	Infection	Method	Treatment group 1	Treatment group 2	Treatment group 3	Included patients (*n*)	Results	Comments
Casey JR Pediatr Infect Dis J 2005 [13]	Tonsillitis	Meta-analysis						
Chow AW, (IDSA) Clin Infect Dis 2012 [3]	Acute sinusitis							
Cohen R Pediatr Infect Dis J 1996 [18]	Tonsillitis		Amoxicillin, 6 days	Penicillin V, 10 days		320	No significant difference	Robust primary endpoint: GAS eradication
Cohen R Pediatr Infect Dis J 2000 [11]	AOM		5 days Amoxicillin–clavulanic acid	10 days Amoxicillin–clavulanic acid		450	Superiority of the 10-day treatment in children aged below 2 years	Double-blind study Stronger difference among children spending the day in daycare center services
Cohen R J Pediatr 1998 [12]	AOM	Multicenter randomized double-blind study	5 days Cefpodoxime	10 days Cefpodoxime		385	Superiority of the 10-day treatment in children aged below 2 years	Double-blind study Stronger difference among children spending the day in daycare center services
DeMuri GP N Engl J Med 2012 [15]	Acute sinusitis	Literature review					Antibiotics are still recommended for pediatric rhinosinusitis No study evaluating short treatment durations	
Hoberman A Pediatr Infect Dis J 2000 [4]	AOM	Literature review					Superiority of the 10-day treatment in children aged below 2 years	
Kozyrskyj A Cochrane rev 2010 [9]	AOM	Cochrane review					5 days seemed to be enough for most children	
Kozyrskyj AL JAMA 1998 [5]	AOM	Meta-analysis					5 days seemed to be enough for most children	

Table 2 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	Treatment group 3	Included patients (*n*)	Results	Comments
Lemiengre MB Cochrane Rev 2012 [10]	Adult acute sinusitis	Cochrane review					Antibiotics were shown to be useless for most adults presenting with uncomplicated rhinosinusitis	
Peyramond D Scand J Infect Dis 1996 [16]	Adult tonsillitis	Randomized multicenter Open-label study	Amoxicillin, 6 days	Penicillin V, 10 days		300		
Pichichero ME Diagn Microbiol Infect Dis 2007 [14]	Adult tonsillitis	Meta-analysis	2nd and 3rd-generation cephalosporins	Penicillin V, 10 days			Non-inferiority of the 5-day treatment with cephalosporins	
Pichichero ME Pediatr Infect Dis J 1997 [6]	Tonsillitis, AOM, acute sinusitis	Literature review					Possibility of a short treatment in most cases	
Pichichero ME Otolaryngol Head Neck Surg 2001 [7]	AOM	Prospective study	5 days	7 days	10 days		Possibility of a short treatment in most cases, except for: patients below 2 years of age; recurrent AOM-AOM associated with otorrhea	Observational non-randomized study
RBP AFSSAPS 2011 [8]	Adult and pediatric upper respiratory tract infections						5 days for patients above 2 years of age 10 days for patients below 2 years of age	
Venekamp RP Cochrane rev 2015 [17]	Pediatric AOM	Cochrane review					Most AOM patients did not need antibiotic therapy, except patients under the age of 2 and patients presenting with otorrhea	

GAS: group A streptococci; AOM: acute otitis media.

respiratory tract infections (2010), and literature analysis on PubMed from 2011 to 2015.

The literature analysis focused on clinical trials comparing the efficacy of a single antibiotic (included in the list of recommended antibiotics) but with different treatment durations.

Current guidelines [19] recommend a 7- to 14-day treatment duration for community-acquired pneumonia; the same recommendation applies for exacerbations of chronic obstructive pulmonary disease (COPD) (average of 10 days). It must be reminded that prescribing antibiotics to pneumonia patients only helps the host's defense mechanisms, as highlighted in an editorial published by Richard Wunderink [20]. Some authors showed that an inadequate/excessive inflammatory response could be responsible for the patient's death, despite microbiological cure. Several authors pointed to the role of treatment duration in the selection of resistant bacteria [21,22] in studies where the risk of post-treatment resistant pneumococcal carriage in children presenting with respiratory tract infections was reduced during short amoxicillin treatments. Besides, the authors of an earlier study showed the clear correlation between low doses of antibiotics, prolonged treatment duration, and the development of bacterial resistance [22].

4.1. COPD exacerbations

National guidelines report a usual treatment duration of 7 to 14 days (average of 10 days) [19]. A limited number of agents can be used with shorter treatment durations: streptogramins (4 days), azithromycin (5 days), clarithromycin (5 days). However, in 2008, Falagas et al. published a meta-analysis of 3083 patients enrolled in seven randomized controlled trials, and showed treatment equivalence between a short 5-day treatment and a longer treatment of 7 to 10 days [23].

4.2. Community-acquired pneumonia

Dunbar et al. compared a 5-day and a 10-day treatment with levofloxacin in a double-blind randomized prospective study [24]. Their findings highlighted the equivalence of both treatment groups, with a limit in the conclusion regarding the different levofloxacin doses (500 mg in the 10-day group and 750 mg in the 5-day group). Indeed, levofloxacin activity is related to the ratio between the area under the curve and the pathogen MIC. This problematic has already been discussed in an editorial [25]. The authors of a subgroup analysis of the population aged over 65 years also did not observe any differences between both treatment groups. However, the same limit in the conclusion as for the core study was raised [26]. The authors of another subgroup analysis of patients presenting with severe pneumonia (Pneumonia Severity Index III and IV) did not observe any differences in terms of clinical or microbiological success, except for a higher incidence of fever resolution after three days in the group receiving the 750 mg dose [27].

The use of macrolides with particularly long half-lives also helped in improving compliance. Drehobl et al. performed an international randomized double-blind study comparing a single-dose microsphere formulation of azithromycin with 7 days of clarithromycin. They did not observe any significant differences between both groups [28]. Another study aimed to compare that same formulation of azithromycin with a 7-day levofloxacin treatment at 500 mg daily. The authors did not observe any differences in terms of clinical success or bacteriological eradication [29]. The single-dose treatment was not exactly similar to a short treatment as the agent's half-life was estimated at 60 hours. However, a summary of these two studies concluded that this single-dose administration of azithromycin was an interesting alternative to a 7-day treatment with levofloxacin [30].

These studies highlight the benefit and feasibility of a shorter antibiotic therapy; however, they do not help in defining the target population of patients. Two strategies can be implemented to suggest a short treatment: a two-step clinical reevaluation or the use of biomarkers, procalcitonin (PCT) being the most frequently studied.

β-lactam antibiotics remain the standard treatment for pneumonia in France. The authors of a prospective randomized double-blind study of adult mild to moderate pneumonia evaluated the administration of amoxicillin for 3 versus 8 days [31]. A treatment switch to oral placebo or oral amoxicillin was offered to patients whose clinical status improved on Day 3 (use of a composite score). Study results showed the non-inferiority of the 3-day treatment in terms of success rates at D10 and D28, clinical resolution, and radiographic outcome. Leophonte et al. compared the administration of ceftriaxone for 5 versus 10 days and observed an equivalence between both treatment groups [32].

An interesting way to reduce both the initial prescriptions of antibiotics and the antibiotic therapy durations would be to correlate it with an inflammation biomarker. Christ-Crain et al. evaluated the usefulness of PCT testing on initial antibiotic prescriptions and on antibiotic discontinuations [33]. Results from their study of 302 consecutive patients showed a significant reduction in initial antibiotic prescriptions (from 99 to 85%) and above all a significant reduction in antibiotic therapy durations, from 12 to 5 days. This data had already been observed in the core study of 925 patients, with a PCT level-guided reduction in treatment durations from 10.7 days to 7.2 days [34]. Other study findings confirmed these results [33,35,36]. The main issue with using PCT is the excessive cost of analysis, ranging from 10 to 54 dollars per patient [37], and an inappropriate use of the test by healthcare professionals. The authors of a Cochrane study assessed 14 studies of 4221 patients overall. They did not observe any differences in terms of mortality or treatment failures [38]. The PCT level-guided antibiotic therapy duration group was associated with a significant reduction in the number of antibiotic exposure days: from 8 to 4 days.

Li et al. [39] published a meta-analysis in 2007 where they regrouped 15 randomized clinical trials (azithromycin 10, β-lactam antibiotics 2, fluoroquinolones 2, and ketolides 1). The authors did not observe any significant differences between short and long-term treatments in terms of risk of treatment failure, mortality, or bacteriological eradication. They suggested that a 7-day treatment, or even a shorter one, could be considered for patients presenting with mild to moderate pneumonia. In 2008, Dimopoulos et al. performed another meta-analysis of

randomized studies comparing short treatments (< 7 days) and long-term ones (> 2 days of difference) using the same agent and the same dosing regimens [40]. The meta-analysis included five adult studies and two pediatric ones. No difference was observed between a short treatment (adults 3–7 days, children 3 days) and a long-term one (adults 7–10 days, children 5 days) in terms of clinical success, long-term follow-up, and microbiological response.

Another way of prescribing shorter treatments would be to improve prescribers' knowledge. Avdic et al. performed a before/after prospective monocentric study and observed that training prescribers helped in significantly reducing treatment duration [41]. No efficacy data was, however, available in this study.

Murray et al. also performed a before/after study to evaluate the benefit of a set of measures including the systematic discontinuation of antibiotics, a treatment duration correlated with CURB-65 criteria, and direct interactions with physicians [42]. A moderate reduction in treatment duration was observed: from 8.3 days to 6.8 days.

Pediatric guidelines for non-severe pneumonia recommend treatment durations from 3 to 14 days, while the World Health Organization (WHO) recommends a 5-day treatment [43]. Only one prospective randomized double-blind comparative study has been performed in this area. The study evaluated children aged 6 months to 5 years presenting with alveolar pneumonia suspected to be of pneumococcal origin and treated with amoxicillin. Success rate was not significantly different between the 5-day and 10-day antibiotic treatments, while a 3-day treatment seemed to be enough [44].

The main characteristics of studies considered in this analysis are presented in Table 3.

4.3. Conclusion

Studies focusing on COPD exacerbation are scare but it seems reasonable to suggest a short treatment of 5 days as it did not prove inferior to a 7- to 10-day treatment in several randomized studies.

Available studies on community-acquired pneumonia drive the recommendation of a 7-day treatment; however, available data cannot lead to the recommendation of a shorter treatment duration.

5. Central venous catheter-related bacteremia (CRB)

Suggested treatment durations:

- 5 days: coagulase-negative staphylococci CRB, following catheter removal;
- 7 days: CRB caused by *Streptococcus*, *Enterococcus*, and Gram-negative bacilli, following catheter removal;
- 10 days: (+ antibiotic lock therapy): CRB without catheter removal, UNLESS *S. aureus* CRB;
- 14 days: *S. aureus* CRB, following catheter removal;
- 21 days: infected thrombosis.

NB – Treatment duration may be modified for secondary localization or infective endocarditis.

Method.– Source: 2001 Northern American guidelines on the management of central venous catheter-related bacteremia (CRB) [54], 2002 French Intensive Care Society guidelines (French acronym SRLF) [55], and literature analysis on PubMed from 2011 to 2015.

When these guidelines did not discuss specific infections, we looked for expert recommendations or literature reviews.

The choice of treatment durations either relies on early randomized studies conducted in the 1990s or on expert opinion. Little recent comparative data is currently available on treatment durations, except for *Staphylococcus aureus* (SA) CRB [56–58].

Guidelines only recommend a short treatment in the absence of bacteremia complications, defined as:

- a favorable outcome after 48–72 hours of treatment (favorable clinical and biological outcome with negative blood cultures);
- absence of infected thrombosis;
- absence of endocarditis or other infectious metastases that would require a prolonged treatment duration.

Data is available on patients at higher risk of complicated presentations (prosthesis, diabetes, or cancer patients) [56,59], but guidelines do not mention this information.

5.1. Uncomplicated S. aureus CRB: 14-day treatment with catheter removal

Treatment administered for less than 14 days is associated with a higher incidence of complications (relapse, secondary localizations) [56,59].

5.2. Uncomplicated CRB caused by coagulase-negative staphylococci (CoNS), Streptococcus, Enterococcus, and Gram-negative bacilli

No study has so far been conducted to compare treatment durations in these types of CRB. Guidelines issued for these infections usually recommend ranges of treatment duration based on expert advice.

The main treatment durations suggested by causative agents are presented in Table 4.

The main characteristics of studies considered in this analysis are presented in Table 5.

Table 3
References – lower respiratory tract infections.
Bibliographie – infections respiratoires basses.

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Comments
Studies comparing various antibiotics							
El Moussaoui [31]	CAP PSI < 110	Randomized double-blind non-inferiority study	AMX 3 days	AMX 8 days	63/56	CR: 93% at D10 in both groups Similar radiological success rate and similar time to symptom resolution	Non-inferiority of the 3-day versus 8-day regimens
Niederman [45] Tellier [46]	CAP	Multicenter randomized double-blind study	TEL 800 mg 5 days or 7 days	CLA 500 mg/d, 10 days	5 days 193 7 days 195 10 days 187	Similar CR observed in the 3 groups Better treatment compliance in the 5-day treatment group	
Drehobl [28]	Adult moderate to mildly severe CAP	Multinational multicenter randomized double-blind study	AZT 2 g, one intake (A)	CLA ER 1 g/d, 7 days (C)	202/209	CR: 92.6% (A) vs. 94.7% (C) (NS)	AZT has a 60-hour half-life; the single-dose probably corresponds to a short treatment of 3-4 days
D'Ignazio [29]	Adult CAP, Fine score I, II, III	Randomized double-blind study	AZT 2 g, one intake (A)	LEV 500 mg/d, 7 days (L)	213/214	CR: 89.7% (A) vs. 93.7% (L) (NS) BE: 90.7% (A) vs. 92.3% (L) (NS)	
Dunbar [24]	CAP	Multicenter randomized, double-blind study	LEV 750 mg/d, 5 days	LEV 500 mg/d, 10 days	198/192	CR: 92.4% (5 days) vs. 91.1% (10 days) (NS) BE: 93.2% (5 days) vs. 92.4% (10 days) (NS)	Main bias: modification of two parameters (duration and dosage)
Shorr [26]	CAP > 65 years	Multicenter, randomized, double-blind, retrospective study	LEV 750 mg/d, 5 days	LEV 500 mg/d, 10 days	80/97	CR: 89% (5 days) vs. 91.9% (10 days) (NS) BE: 90.3% (5 days) vs. 87.5% (10 days) (NS)	Subgroup analysis of Dunbar's study [6] Patients treated for 5 days were older and presented with a more severe infection High doses were well-tolerated
Shorr [27]	CAP, Fine score III & IV	Retrospective study	LEV 750 mg/d, 5 days	LEV 500 mg/d, 10 days	76/83	CR: 90.8% vs. 85.5% (NS) BE: 88.9% vs. 87.5% (NS) Resolution of fever at D3: 48.4% vs. 34% (P<0.05)	Subgroup analysis of Dunbar's study [6]

Table 3 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Comments
Antibiotic prophylaxis correlated with CRP							
Cals [47]	Lower respiratory tract infection	Pragmatic, randomized, controlled, cluster study	Prescription with CRP measurement ± training	Prescription without CRP measurement ± training	CRP 110 Training 84 CRP + training 117 Standard 120	CRP ± training group: reduction in initial prescriptions (52.9 to 30.8%, $P = 0.02$), reduction in antibiotics prescribed within 28 days (58.3 vs. 44.9%, $P < 0.01$), no difference in terms of new consultations at 28 days	Training/information for FPs Only one CRP measurement On the basis of studied criteria, training seemed to be more efficient than the use of CRP No clinical recovery data
Cals [48]	Lower respiratory tract infection and rhinosinusitis	Controlled randomized study 32 FPs	Prescription correlated with CRP	Control group	129/129	Reduction in initial prescriptions from 51 to 41% in the CRP group Reduction in antibiotic exposure within 28 days (from 58.8% to 46.4%)	No assessment of antibiotic therapy duration No clinical recovery data
Diederichsen [49]	Respiratory tract infection	Controlled randomized study	Prescription correlated with CRP	Standard group	Control group 398 CRP 414	No reduction in prescription (46% in the control group vs. 43%) Higher morbidity in the CRP group (12 vs. 8%, $P = 0.05$)	No clinical recovery data
Antibiotic therapy correlated with PCT level							
Christ-Crain [33]	CAP	Randomized study	Conventional antibiotic therapy	Antibiotic therapy correlated with PCT level	151/151	Reduction in initial prescriptions (85% vs. 99%) Reduction in treatment durations (5 vs. 12 days)	No clinical recovery data
Long [35]	Adult CAP Class I–III PSI	Randomized controlled study	Standard treatment	PCT level-guided treatment	86/86	CR: 85.2% vs. 88.9% (NS) Per protocol: reduction of two days in the mean antibiotic therapy duration: 5 days vs. 7 days ($P < 0.001$)	Cut off PCT < 0.1 mg/l No details on antibiotics used
Kristoferssen [36]	Adult CAP	Multicenter randomized controlled study	Standard treatment	PCT level-guided treatment	110/113	25% reduction in treatment duration in the PCT group (6.8 days to 5.1 days, $P = 0.007$)	If PCT < 0.25 µg/L: treatment discontinuation No treatment response data Daily PCT measurement
Christ-Crain [53]	Lower respiratory tract infection	Monocentric, prospective, randomized, single-blind study	Standard treatment	PCT level-guided treatment	119/124 45/42 CAP 31/29 COPD	Treatment duration reduction in the PCT group, all infections (10.9 vs. 12.8 days, $P = 0.03$). Reduction in initial prescriptions (83% vs. 44%, $P < 0.0001$) COPD group: no difference in terms of mortality and readmission. Similar treatment duration but fewer antibiotics prescribed (87% vs. 38%, $P < 0.001$) No difference in terms of mortality	No clinical recovery data

Table 3 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Comments
Schuetz [38]	Lower respiratory tract infection	Multicenter controlled randomized study Non-inferiority study	Prescription without PCT	Prescription with PCT	694 without PCT 687 with PCT	PCT group: prescription reduction (87.7 vs. 75.4%), reduction in antibiotic therapy duration (8.7 vs. 5.7 days) CAP group: prescription reduction (99.1 vs. 90.7%), reduction in antibiotic therapy duration (10.7 vs. 7.2 days) COPD group: prescription reduction (69.9 vs. 48.7%), reduction in antibiotic therapy duration (5.1 vs. 2.5 days)	Objective: to reduce the use of antibiotics No clinical recovery data
Stolz [50]	COPD	Monocentric randomized controlled study	PCT level-guided prescription	Standard group	113/113	Similar clinical success Reduction in initial prescriptions from 72% to 40% ($P < 0.0001$) Significant reduction in antibiotic therapy durations	Main objective: treatment duration PCT level reevaluation within 24 hours
Albrich [51]	Lower respiratory tract infection	Observational study			1520 patients assessed	The algorithm helped in reducing antibiotic therapy duration from 7.4 to 5.9 days ($P < 0.001$)	Outpatients and patients treated in the emergency department Modification according to a PCT level-based decisional algorithm
Briel [52]	Respiratory tract infection	Non-inferiority multicenter open-label randomized study	PCT level-guided prescription	Control group	PCT 231 Control group 224	Antibiotic prescription reduction from 97% to 25% (72% reduction); 40% reduction for pneumonia Mean treatment duration decreased from 7.1 to 6.2 days in the PCT group	Limitation: mix of upper and lower respiratory tract infections No clinical recovery data
Avdic [41]	CAP	Before/after study			62/65	Antibiotic therapy duration decreased from 10 to 7 days ($P < 0.001$)	Intervention based on educating and raising awareness of the benefit of reducing antibiotic therapy duration No efficacy data

CAP: community-acquired pneumonia, PSI: pneumonia severity index, AMX: amoxicillin, CR: clinical recovery, TEL: telithromycin, CLA: clarithromycin, AZT: azithromycin, LEV: levofloxacin, BE: bacteriological eradication, CRP: C-reactive protein, PCT: procalcitonin, COPD: chronic obstructive pulmonary disease, FP: family physicians, NS: non-significant.

Table 4
Treatment durations for central venous catheter-related bacteremia.
Durées de traitement pour les bactériémies liées aux cathéters veineux centraux.

Type of infection	Duration of conventional treatment[a]	Short treatment[a]	Target population for a short treatment	Evidence required for a short treatment	Comments
Uncomplicated CRB					
Staphylococcus aureus	14 days to 6 weeks	14 days	Favorable outcome at 72 hours (clinical outcome + negative blood cultures + absence of endocarditis)	Retrospective data, case series [56–58]	Catheter ablation required
Coagulase-negative staphylococci	5 to 7 days 10 to 14 days + ALT	5 days 10 days + ALT	Catheter ablation No catheter removal with ALT	Expert advice: absence of literature data	Catheter ablation without antibiotic therapy is sometimes enough
Streptococci, enterococci, Gram-negative bacilli	7 to 14 days 10 to 14 days + ALT	7 days 10 days + ALT	Catheter ablation No catheter removal	Expert advice: absence of literature data	For *Pseudomonas aeruginosa* and related bacteria: catheter ablation should be favored
Complicated CRB					
Infected thrombosis	3 to 6 weeks	3 weeks		Expert advice: absence of literature data	
Other (infective endocarditis, secondary localization)	Based on the complication observed				

CRB: central venous catheter-related bacteremia; ALT: antibiotic lock therapy.
[a] Antibiotic therapy duration is calculated from the day of catheter removal onwards.

Table 5
References – central venous catheter-related bacteremia (CRB).
Bibliographie – bactériémies liées aux cathéters veineux centraux.

Reference	Infection	Method	Study treatment	Comparator	Sample size	Results	Comments
Mermel, 2009 [54]	CRB	IDSA guidelines					
Ghanem, 2007 [59]	*S. aureus* CRB in cancer patients	Monocentric retrospective case series	Effective antistaphylococcal therapy	14 days	91	3-month follow-up	No specific analysis of treatment duration Increased incidence of complications in this population of patients (19% of thrombosis cases, 21% of septic embolism cases) → a long-term treatment is useful for these patients
Pigrau, 2003 [56]	*S. aureus* CRB (+ *S. aureus* bacteremia)	Monocentric retrospective case series	21 cloxacillin 5 amoxicillin 3 piperacillin-tazobactam 21 vancomycin 2 co-trimoxazole	10–14 days	87 CRB (and 20 bacteremia), subgroup of 64 uncomplicated episodes	Efficacy of the short treatment in the absence of IE or relapse at 3 months in the uncomplicated CRB and *S. aureus* bacteremia groups	Exclusion of IE/early deaths/persistent hyperthermia at 72 hours/infectious metastases
Zeylemaker, 2001 [58]	*S. aureus* CRB	Monocentric retrospective case series	Effective antistaphylococcal therapy	1–14 days vs. > 14 days	49	49% of complications at 1 year, non-correlated with treatment duration	
Malanoski, 1995 [60]	*S. aureus* CRB	Monocentric retrospective case series	14 β-lactam 35 vancomycin	10–14 days vs. > 14 days	50	No significant differences in terms of relapse for uncomplicated episodes at 3 months 2 relapses observed in 3 patients treated for < 10 days	Exclusion of patients presenting with IE and early complications (septic embolism, death)
Raad, 1992 [57]	*S. aureus* CRB	Retrospective multicenter case series + literature review	Effective antistaphylococcal treatment	< 10 days vs. 10–14 days	46	Favorable outcome at 1 year for the 28 episodes treated for 10-14 days, 3 relapses observed in 18 patients treated for < 10 days	Exclusion of patients presenting with IE and bone and joint localizations Fever or blood cultures + persistence at 72 hours associated with treatment failure
Ehni, 1989 [61]	*S. aureus* CRB	Prospective monocentric case series	Effective antistaphylococcal treatment	< 15 days	13	12 favorable outcomes, 1 relapse with IE at 3 months	
Mylotte, 1987 [62]	*S. aureus* CRB	Prospective monocentric case series	Effective antistaphylococcal treatment	> 14 days	114	Low incidence of IE/septic embolism	
Mylotte, 1987 [63]	*S. aureus* CRB	Prospective monocentric case series	10 nafcillin 4 cefazolin 8 vancomycin	≤ 14	28	Favorable outcome for the 22 patients treated with a short treatment	Exclusion of patients presenting with IE, and early death
Iannini, 1976 [64]	*S. aureus* bacteremia + device	Retrospective monocentric case series	Effective antistaphylococcal treatment	3–21 days	22	Favorable outcome at 3 months	Exclusion of patients presenting with IE

CRB: central venous catheter-related bacteremia; IE: infective endocarditis.

6. Uncomplicated primary bacteremia

Suggested treatment durations:
In the absence of infective endocarditis and secondary localization:

- 5 days: coagulase-negative staphylococci, oral streptococci;
- 7 days: Enterobacteriaceae, enterococci;
- 10 days: non-fermentative Gram-negative bacilli;
- 14 days: *S. aureus* and *S. lugdunensis*.

Method: considering the absence of specific guidelines, we conducted a literature analysis on PubMed from 2005 to 2015.

Little data is available on antibiotic therapy duration, and available data is quite varied and hard to use. Data is heterogeneous with regard to populations of patients (children, adults, intensive care patients, etc.), clinical situations (catheter-related bacteremia, bacteremia caused by an organ infection, primary bacteremia, i.e. without any known infectious sites), causative agents, but also with methods and durations of "short treatment" that may vary from less than 5 days to less than 10 days [65–71]. There is also no specific guideline on the management of bacteremia (except for CRB).

Nevertheless, the analysis of current data enables us to suggest, based on a satisfactory level of evidence (prospective data obtained with an appropriate method), that uncomplicated (without any secondary localization, infective endocarditis, infected thrombophlebitis nor any intravascular device-related infection) *S. aureus* bacteremia (susceptible or resistant to methicillin) with an initially favorable outcome within 72 hours may be treated with a 14-day treatment. Shorter treatments significantly increase the risk of relapse (> 5%) [65].

A 14-day treatment (by analogy with *S. aureus*) may be suggested considering the characteristics and prognosis of *S. lugdunensis* bacteremia (absence of specific literature data).

Treatment durations suggested for uncomplicated primary bacteremia rely on expert advice [66], descriptive retrospective data [67–69,71], a meta-analysis of heterogeneous studies [70], and on available CRB data (Table 6).

Well-conducted studies focusing on bacteremia patients, such as the BALANCE study, are thus needed [72].

The main characteristics of studies considered in this analysis are presented in Table 7.

7. Infective endocarditis (except in case of surgery) and implantable pacemakers (PM) and implantable cardioverter defibrillator (ICD)-related infections

7.1. Infective endocarditis (IE)

Method.– 2009 and 2015 European guidelines [73,74], and literature analysis on PubMed from 2005 to 2015. When these guidelines did not discuss specific infections, we looked for expert recommendations or literature reviews.

Suggested treatment durations:

- 1 week:
  - removed PM- or ICD-related uncomplicated bacteremia, except for *S. aureus* bacteremia;
- 2 weeks:
  - removed PM- or ICD-related uncomplicated bacteremia caused by *S. aureus*,
  - penicillin-susceptible streptococcal infective endocarditis, if combination of β-lactam and aminoglycoside;
- 4 weeks:
  - uncomplicated native valve infective endocarditis,
  - removed PM- or ICD-related infective endocarditis;
- 6 weeks:
  - prosthetic valve infective endocarditis,
  - non-removable PM- or ICD-related bacteremia.

NB: treatment duration may be modified for a secondary localization.

Treatment durations recommended in the 2009 and 2015 European guidelines [73,74] are also mentioned in the Northern American guidelines [75,76]. Treatment durations are either based on early randomized studies conducted in the 1990s or on expert opinion. Recent comparative data on treatment durations is scarce, except for retrospective data on aminoglycoside treatment duration in enterococcal infective endocarditis [77,78].

Table 8 presents treatment durations suggested for uncomplicated infective endocarditis (absence of surgical indication, absence of bone and joint septic localization) caused by bacteria susceptible to standard β-lactams.

The following short treatments are the only validated ones for native valve infective endocarditis:

- dual combination therapy with IV β-lactam and gentamicin for two weeks for uncomplicated infective endocarditis caused by penicillin-susceptible oral streptococci [79]. This combination therapy containing two weeks of an aminoglycoside is associated with an increased toxicity (renal and cochlear) compared with the conventional treatment (IV β-lactams for four weeks);
- two weeks of IV penicillin M monotherapy for right-sided infective endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) [80,81].

For other situations, no study has compared a 4-week treatment with a 6-week treatment with β-lactams; and no data suggests the superiority of the 6-week treatment.

Table 6
Treatment durations – primary uncomplicated bacteremia[a].
Durées de traitement – bactériémies primaires non compliquées.

Type of infection	Suggested treatment duration (days)	Target population for a short treatment	Evidence required for a short treatment	Comments
S. aureus	14	Rapidly favorable outcome (<72 hours) Absence of secondary localization, IE, and infected thrombosis If catheter: catheter ablation	Non-randomized prospective data (appropriate method)	
Coagulase-negative staphylococci	5		Expert advice	
Enterococci	7		Expert advice	
Oral streptococci	5		Expert advice	
Enterobacteriaceae	7		Expert advice	
Non-fermentative GNB	10		Expert advice	

GNB: Gram-negative bacilli; IE: infective endocarditis.
[a] For complicated primary bacteremia, please refer to the treatment suggested for the complication

With regard to aminoglycosides:

- for streptococcal IE, they are only useful in the short treatment of infective endocarditis and in patients allergic to β-lactams;
- their benefit is disputed in MSSA infective endocarditis as no clinical study has so far demonstrated any significant differences between a β-lactam monotherapy and a dual combination therapy with β-lactams and an aminoglycoside [82,83]. These studies lack statistical power to come to any conclusion. Experimental data (*in vitro* and animal studies) also favors the addition of an aminoglycoside. The 2015 European guidelines no longer recommend the use of aminoglycosides in the treatment of MSSA infective endocarditis;
- aminoglycoside administration may be limited to two weeks in enterococcal infective endocarditis (well-conducted retrospective studies, such as "before/after" cohort studies) [77,78].

There is a strong consensus for a 6-week treatment for prosthetic valve infective endocarditis because of the biofilm presence.

7.2. PM- and ICD-related bacteremia

Method: research based on the 2015 British guidelines [84], and on a literature analysis on PubMed from 2005 to 2015.

Very little literature data is available on treatment durations for this type of infections.

Recent British guidelines [84] suggest the following treatment modalities, with a poor level of evidence (case series, heterogeneous retrospective studies) (Table 8):

- in the absence of infective endocarditis or secondary localization and following device removal (PM or ICD): 1 or 2 week(s) of antibiotic therapy;
- in the presence of infective endocarditis and device removal: similar treatment duration as for infective endocarditis;
- if the device (PM or ICD) cannot be removed: 6-week antibiotic therapy, followed by blood culture control at treatment discontinuation. A longer treatment duration or even a suppressive treatment may be discussed in case of bacteremia relapse.

The main characteristics of studies considered for the analysis of infective endocarditis and PM/ICD-related bacteremia treatment durations are presented in Table 9.

8. Bacterial meningitis

Suggested treatment durations:

- 5 days:
  - *N. meningitidis* meningitis;
- 7 days:
  - *H. influenzae* meningitis,
  - *S. pneumoniae* meningitis;
- 14 days: *S. agalactiae* meningitis;
- 21 days:
  - *L. monocytogenes* meningitis,
  - Gram-negative bacilli meningitis, except for *H. influenza* meningitis.

Method: 2004 American guidelines [91] and 2009 French guidelines [92]. PubMed search using the following search terms: "meningitis", "bacterial meningitis", "pneumococcal meningitis", "meningococcal meningitis", "*Haemophilus influenzae* meningitis", "*Streptococcus pneumoniae*", "*Neisseria meningitidis*", "*Haemophilus influenzae*", "*Nosocomial meningitis*", "duration of treatment".

Treatment duration for bacterial meningitis rather relies on prescriber habits than on reliable clinical trial. Two guidelines (Northern American and French ones) suggest specific treatment durations. A few clinical trials have been conducted after the publication of these guidelines, and thus fine-tune the

Table 7
References – primary uncomplicated bacteremia.
Bibliographie – bactériémies primaires non compliquées.

Reference	Infection	Method	Study treatment	Comparator	Sample size	Results	Comments
Corona 2004 [67]/Corona 2006 [68]	Community-acquired bacteremia + healthcare-associated bacteremia Intensive care Exclusion of IE and bone and joint infections	Prospective (6 months in 2000), observational, monocentric study	≤5 days	>5 days	102 bacteremia episodes, 84 patients	Only descriptive: short treatment for 78 patients (73.5%): 57% of community-acquired bacteremia, 79% of hospital-acquired bacteremia, and 80% of intensive care-acquired bacteremia	No outcome analysis Miscellaneous
Corey 2009 [66]	Bacteremia in immunocompetent patients	Literature review					
Havey 2011 [70]	Intensive care Neonatology, urinary tract infection, intra-abdominal infection, pneumonitis All bacteria	Systematic literature review + meta-analysis (24 controlled studies 1947-2010, 7 included in the analysis, only 1 study focused on neonatal bacteremia)	5 to 7 days	7 to 21 days	155 bacteremia patients (7 studies) 28 patients treated with a "short treatment" 32 patients treated with a "long-term treatment"	No significant differences (clinical recovery, microbiological recovery, and mortality)	Very little data on the specific item "bacteremia" Treatment duration could only be assessed in 60 patients Numerous pediatric data Highly miscellaneous Short treatment <7 days
Chong 2013 [65]	Uncomplicated *S. aureus* bacteremia	Prospective cohort – observational and monocentric – Korea 2008–2010	<14 days	≥14 days	111 (38/73)	At 12 weeks: no significant differences in terms of treatment failure (26.3% vs. 21.9%) or mortality (18.4% vs. 21.9%) More relapses in the "short treatment" group (7.9% vs. 0, $P=0.04$)	47.7% MRSA 46.9% + 27.9% catheter-related bacteremia (central, peripheral) Treatment duration does not include oral antibiotics No explanation of treatment duration above 14 days
Park 2014 [71]	Uncomplicated bacteremia Gram-negative bacilli Children	Retrospective and monocentric, 2002–2012 (propensity score analysis and then logistical regression)	7 to 10 days	>10 days	183/501 Logistical regression 170/170	No significant differences in terms of microbiological relapse	*Median duration of short treatment = 10 days* *2/3 CRBs: bias = absence of catheter removal or catheter removal* *11% of P. aeruginosa*
De Santis 2015 [69]	Community-acquired bacteremia + healthcare-associated bacteremia Intensive care Exclusion of IE and bone and joint infections	Retrospective: 2000 (above-mentioned study) vs. 2013 (6 months of retrospective data collection) comparison	≤5 days	>5 days	113 bacteremia episodes, 87 patients	Short treatment for 65.7%	Descriptive, no outcome analysis Miscellaneous

IE: infective endocarditis; CRB: central venous catheter-related bacteremia; MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 8
Treatment durations – infective endocarditis and pacemaker- and implantable cardioverter defibrillator-related infections.
Durées de traitement – endocardites infectieuses et infections sur pacemakers et défibrillateurs.

Type of infection	Duration of conventional treatment	Short treatment	Target population for a short treatment	Evidence required for a short treatment	Comments
Infective endocarditis			Absence of secondary infectious localization requiring a longer treatment Absence of surgical indication		
Native valve					
Streptococci	4 weeks of β-lactam alone	2 weeks of β-lactam + gentamicin	Oral *Streptococcus* susceptible to amoxicillin	Randomized study (1995)	Increased toxicity with aminoglycosides
Enterococci	4 to 6 weeks of amoxicillin + 2 to 4 weeks of gentamicin	4 weeks of amoxicillin + 2 weeks of gentamicin		Expert advice: no data 4 vs. 6 weeks aminoglycoside duration: retrospective (cohorts) (2002 and 2013)	Alternative: amoxicillin + ceftriaxone for 6 weeks
MSSA	4 to 6 weeks of penicillin M	4 weeks of penicillin M		Expert advice: no data 4 vs. 6 weeks of penicillin M No clinical data supporting the use of aminoglycosides	
		2 weeks of penicillin M alone	Uncomplicated right-sided IE	Randomized studies (1994 and 1996)	
Prosthetic valves	6 weeks			Expert advice	Biofilm
Pacemaker and implantable cardioverter defibrillator-related bacteremia					
	6 weeks	1 week after PM or ICD removal, except for *S. aureus* bacteremia: 2 weeks.	In the absence of prosthetic valve IE and removed PM or ICD	Low (miscellaneous studies, case series)	
	>6 weeks, or even treatment that only keeps symptoms at bay	6 weeks	If no device removal	Low (case series)	

IE: infective endocarditis; PM: pacemaker; ICD: implantable cardioverter defibrillator; MSSA: methicillin-sensitive *Staphylococcus aureus*.

suggestions. However, treatment duration must be tailored to the clinical presentation of each patient.

8.1. IDSA guidelines [91]

Treatment durations by causative agents are presented in Table 10 (A-III).

The recommended treatment duration in newborns is two weeks following the first lumbar puncture with sterile cerebrospinal fluid (CSF) or three weeks overall.

8.2. SPILF guidelines [92]

Treatment durations recommended by causative agents are presented in Table 10.

In the absence of microbiological documentation and if the bacterial meningitis diagnosis is still suspected (absence of alternative diagnosis; suggestive symptoms), the initial antibiotic therapy is continued for 14 days if the outcome is favorable.

8.3. Clinical trials

Clinical trials (Table 11) considered for drafting the guidelines on *Neisseria meningitidis* meningitis have been performed in low-income endemic countries during *N. meningitidis* epidemics. Considering these specific conditions, a 1 to 3-day treatment with ceftriaxone seemed possible [93,94]. A few studies, performed under similar circumstances after the publication of these guidelines, support the possibility of short treatments, but do not recommend using single-dose regimens.

Table 9
References – infective endocarditis – pacemaker- and implantable cardioverter defibrillator-related infections.
Bibliographie – endocardites infectieuses – infections de pacemakers et défibrillateurs.

Reference	Infection	Method	Study treatment	Comparator	Sample size	Results	Comments
Habib 2009 [73]	IE	European guidelines					
Habib 2015 [74]	IE	European guidelines					
Nishimura 2014 [75]	IE	American guidelines on valvular diseases					
Hoen 2013 [85]	IE	2013 NEJM (updated)					
Sandoe JAC 2015 [84]	PM infections	British guidelines					
Dahl 2013 [78]	Left-sided IE caused by *E. faecalis* (low level of resistance to aminoglycosides)	Before-after (2002-2011; 2007 = new guidelines), monocentric study (Denmark)	Gentamicin, 2 weeks β-lactam, idem	Gentamicin, 4 to 6 weeks β-lactam, idem	41 patients before 2007 vs. 43 after	No significant differences	No data on β-lactam treatment
Leibovici 2010 [83] Based on Sexton 1998 [86], Ribera 1996 [80], Korzeniowski 1982 [87], Abrams 1979 [88], and Coppens 1983 [89]	MSSA bacteremia (1) or IE (3, including 2 in IVDU)	Literature review + meta-analysis (4 randomized studies)					
Ribeira 1996 [80]	MSSA right-sided IE	Randomized, controlled, open-label, multicenter study	14-day cloxacillin monotherapy	Dual combination therapy with cloxacillin (14 days) + gentamicin (7 days)	90 (45/45) intent-to-treat patients 74 (38/36) observations that could be assessed	No significant differences in terms of mortality and recovery	90% HIV+
Abrams 1979 [88]	*S. aureus* right-sided IE	Randomized, controlled, open-label study	Penicillin or cephalosporin monotherapy for 4 weeks	Dual combination therapy with penicillin or cephalosporin for 4 weeks + gentamicin for 2 weeks	25 (12/13) patients	No significant differences in terms of mortality and recovery	100% recovery in patients who did not undergo surgery No nephrotoxicity data
Korzeniowski 1982 [87]	*S. aureus* right-sided and left-sided IE	Randomized, controlled, open-label study	Nafcillin monotherapy for 6 weeks	Dual combination therapy with nafcillin (6 weeks) + gentamicin (2 weeks)	90 IVDU + 60 intent-to-treat non-IVDU patients, 48 (24/24) IVDU + 30 (11/19) non-IVDU that could be assessed	No significant differences in terms of mortality and recovery	

Table 9 (*Continued*)

Reference	Infection	Method	Study treatment	Comparator	Sample size	Results	Comments
Sexton 1998 [86]	*S. viridans* or *S. bovis* left-sided IE	Randomized, controlled, open-label, multicenter study	Ceftriaxone monotherapy for 4 weeks	Dual combination therapy with ceftriaxone (4 weeks) + gentamicin (2 weeks)	51 (26/25) patients	No differences in terms of recovery, mortality, and relapse	
Falagas 2006 [82] Based on Sexton 1998 [86], Ribera 1996 [80], Korzeniowski 1992 [87], Abrams 1979 [88], Rajashekaraiah 1980 [90]		Literature review + meta-analysis (4 randomized studies + 1 comparative prospective study)					Based on 3 randomized studies that were already included in Leibovici's literature review + 2 other studies
Rajashekaraiah 1980 [90]	*S. aureus* left-sided and right-sided IE	Comparative and prospective study	β-lactam monotherapy for 4 to 6 weeks	Dual combination therapy with β-lactam (4 to 6 weeks) + aminoglycoside (7 days)	33 patients (12/21)	No differences in terms of mortality	
Olaison CID 2002 [77]	Enterococcal IE	Prospective cohort study 1995–1999, Norway			93 patients	Median treatment duration in patients who have been cured: B-lactam (42 days), aminoglycosides (15 days)	Mortality 16%, relapse 3%
Francioli 1995 [79]	Oral streptococci	Open-label multicenter study	Ceftriaxone 2 g + netilmicin 4 mg/kg/day, 2 weeks	No comparator (open-label study)	48 patients	42 cured, 5 deaths (without any active infection), 1 relapse	4 renal adverse effects, 1 hearing adverse effect
DiNubile 1994 [81]	Right-sided IE in IVDU patients (MSSA)	Literature review of 3 non-randomized prospective studies					

IE: infective endocarditis; MSSA: methicillin-sensitive *Staphylococcus aureus*; IVDU: intravenous drug users; HIV: human immunodeficiency virus; PM: pacemaker.

Table 10
Treatment durations recommended by the IDSA – bacterial meningitis.
Durées de traitement recommandées par l'IDSA – méningites bactériennes.

Causative agent	Treatment duration recommended by the IDSA	Treatment duration recommended by the SPILF
Neisseria meningitidis	7 days	4 to 7 days[a]
Haemophilus influenzae	7 days	7 days
Streptococcus pneumoniae	10–14 days	10 to 14 days[b]
Streptococcus agalactiae	14–21 days	14 to 21 days
Listeria monocytogenes	21 days	21 days
Gram-negative aerobic bacilli	21 days	–
Escherichia coli	–	21 days

[a] 4 days with a rapidly favorable outcome.
[b] Independently from penicillin MIC. Reducing treatment to 10 days may be possible with a rapidly favorable outcome (within the first 48 hours) and with *S. pneumoniae* strains susceptible to the 3rd-generation cephalosporin used (MIC < 0.5 mg/l).

A meta-analysis of five comparative studies concluded to the equivalence of treatment regimens of 4–7 days and 7–14 days, but the authors could not stratify the results by causative agent [95]. A pediatric clinical trial compared the administration of ceftriaxone for 5 vs. 10 days. The authors observed similar results in both treatment groups [96].

A short treatment (3 to 5 days) for meningococcal bacterial meningitis therefore seems possible as long as the early clinical outcome is favorable. We are, however, lacking data on other bacteria responsible for bacterial meningitis, even though we may observe a similar trend in recommending shorter treatment durations (7 days for pneumococcal meningitis in case of favorable outcome).

9. Intra-abdominal infections (IAI)

Suggested treatment durations:

- ≤ 24 hours:
  - digestive perforation, with surgery,
  - non-perforated appendicitis, with surgery,
  - uncomplicated cholecystitis, with surgery performed within 24 hours;
- 3 days:
  - localized community-acquired peritonitis, with surgery or drainage,[1]
  - angiocholitis, with drainage,
  - acute diarrhea requiring antibiotic therapy;
  - 4 days: generalized community-acquired peritonitis, with surgery or drainage[1];
  - 5 days:
    - community-acquired ascitic fluid infection,
    - typhoid fever (if azithromycin);
  - 8 days:
    - postoperative peritonitis if the empirical antibiotic therapy is active against bacteria isolated during the procedure;
  - 10 days: toxin-secreting *Clostridium difficile* infection.

[1] Infection source control.

Method.– Source: IDSA guidelines on the management of intra-abdominal infections (IAI) [97], French Formal Expert Guidelines [98], and literature analysis on PubMed from 2011 to 2015.

When these guidelines did not discuss specific infections, we looked for expert recommendations or literature reviews.

The antibiotic therapy duration recommended by scientific societies in specific situations (digestive perforation, localized community-acquired peritonitis, etc.) is short and no range of treatment duration is advised [97,98]. A short treatment may be suggested in other situations provided the infection source is adequately controlled. The importance of drainage in IAIs should thus be stressed (surgical or percutaneous). Guidelines cannot be issued for some IAIs as relevant data is lacking (healthcare-associated IAIs) or because of the uncommon nature of the infection (liver abscesses).

It should also be reminded that in case of an IAI negative outcome, looking for complications is wiser than pointlessly continuing the antibiotic therapy as it has been shown that [99] a prolonged antibiotic therapy is associated with an increased risk of extra-abdominal infections and with an excessive case fatality.

9.1. Infections requiring a short antibiotic therapy (≤ 24 hours)

If the infection source is controlled [97]:

- perforation and proximal gastrojejunal wound, colonic perforation following colonoscopy (in case of colon preparation) if the infection source is controlled within 24 hours;
- acute appendicitis with surgery and without any perforation/abscess/localized peritonitis.

9.2. Localized community-acquired peritonitis: ≤ 3 days if the infection source is controlled

The duration suggested by the most recent French Formal Expert Guidelines [98] is 2 to 3 days. The authors of a randomized study [100] showed that, for surgical patients presenting with localized peritonitis whose condition improved on Day 3 (based on three criteria: fever, leukocytosis, and ileus), the recovery rate was similar for patients discontinuing the

Table 11
References – bacterial meningitis.
Bibliographie – méningites bactériennes.

Reference	Method	Treatment group 1	Treatment group 2	Conclusion	Bias	Comments
Molyneux E et al. 2011 [96]	Double-blind, multinational, randomized study Children aged 2 months to 12 years	Ceftriaxone 5 days 496 patients	Ceftriaxone 10 days 508 patients	2 relapses in group 1 (1 HIV-infected patient), 0 relapse in group 2 0 bacteriological failure If favorable clinical outcome, discontinue treatment on Day 5		Common pathogens
Karageorgopoulos DE et al., 2009 [95]	Meta-analysis of 5 pediatric randomized studies Children aged 3 weeks to 16 years	4–7 days Ceftriaxone	7–14 days ceftriaxone	No differences in terms of mortality, immediate sequelae, side effects		Impossible to stratify by bacteria
Nathan N et al. 2005 [93]	Randomized Niger 15% of adults *N. meningitidis* in 95% of cases	Ceftriaxone 1 dose $n = 255$	Chloramphenicol oil suspension, extended release $n = 255$	9% of relapses in both groups, 5% and 6% mortality		No treatment duration comparison
Briggs S et al. 2004 [94]	Retrospective 90 patients included, including 72 confirmed cases of *N. meningitidis* and 18 probable cases	Benzylpenicillin 3 days	No treatment	Mortality: 7%	No comparison	The authors believe that 3 days of ceftriaxone are enough

antibiotic therapy on Day 3 and patients continuing it for longer than five days.

9.3. Generalized community-acquired peritonitis: 4 days if the infection source is controlled

French [98] and Northern American guidelines [97] suggest treatment durations ranging from 5 to 7 days and from 4 to 7 days, respectively. Treatment duration is usually determined based on the improvement of composite criteria (temperature < 38 °C for more than 48 hours, decreased leukocytosis, ileus regression). The analysis of various studies (Table 12), and especially of the recent study conducted by Sawyer [101], shows that a fixed 4-day postoperative antibiotic therapy is not associated with negative clinical consequences (mortality, surgical site infection, and relapse) compared with a treatment duration determined based on the improvement of these criteria. A fixed treatment duration also allows for the significant reduction in antibiotic therapy durations (median of 4 vs. 8 days).

9.4. Nosocomial or healthcare-associated peritonitis

The range of treatment durations suggested by the French Formal Expert Guidelines is particularly broad: 5 to 15 days [98] as there was, at the time, no study comparing various antibiotic therapy durations. Guidelines mention that the infection source control, the absence of complication following successful drainage, and the favorable outcome of the composite criteria described earlier could lead to reducing antibiotic therapy to 5 days. The results of a French study of ICU-hospitalized patients presenting with postoperative peritonitis, released after the publication of the guidelines, showed that an 8-day treatment was similar to a 15-day treatment in terms of clinical response, if the initial empirical antibiotic therapy was active against the bacteria isolated during the procedure [102].

9.5. Diverticulitis

9.5.1. Uncomplicated diverticulitis: no need for an antibiotic therapy

The benefit of the antibiotic therapy is disputed [103–105]. Findings from a randomized study [106] do not show any benefit of the antibiotic therapy in terms of complication reduction, length of hospital stay, and 1-year relapse. A CT scan must be performed to differentiate an uncomplicated diverticulitis from a complicated one (criteria described by Ambrosetti [107]).

9.5.2. Complicated diverticulitis with surgery

Please refer to “community-acquired peritonitis”.

Table 12
Reference – intra-abdominal infections (IAI).
Bibliographie – infections intra-abdominales (IIA).

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Statistics	Comments
Sawyer RG 2015 [101]	Complicated IAI with infection source control	Multicenter, randomized study	Control group (C) Antibiotic therapy duration: 2 days after fever, leukocytosis, and ileus resolution Maximum 10 days	Experimental group (E) Antibiotic therapy duration: 4 ± 1 days	257/260	C: 21.8% vs. E: 22.3% ($P = 0.92$) Duration: 8 days (C) vs. 4 days (E) ($P < 0.001$) Secondary criteria: microbiological relapse or MDRB SSI 3.5% vs. 2.3% ($P = 0.62$)	No differences between both groups with regard to the composite criterion	Main composite criterion at 30 days: SSI, relapse, mortality Only for IAIs with infection source control (surgical or percutaneous drainage: 33% in both groups) Few immunodeficient patients Apache II score of 10: mild patients Non-compliance with protocol: 28% of the C group vs. 18% of the E group ($P = 0.02$)
Riccio LM 2014 [99]	All IAIs	Monocentric retrospective study 1:2 matching on Apache II	Extra-abdominal infection	No extra-abdominal infection	469/938	Median antibiotic therapy duration: 14 vs. 11 days ($P < 0.01$) Mortality: 14.9% vs. 9% ($P < 0.01$)	Antibiotic therapy duration: $P < 0.01$ Mortality: $P < 0.01$ Logistical regression: antibiotic therapy duration – independent predictive factor for extra-abdominal infection ($P < 0.001$)	57% of community-acquired IAIs Retrospective Monocentric
Basoli A 2008 [100]	Localized peritonitis with surgery	Randomized multicenter double-blind study Ertapenem Inclusion at D3 if fever, leukocyte count, and ileus have improved	≥ 5 days	3 days	48/42	89.6% vs. 92.9%	No differences between both groups	Main criterion: clinical recovery at W2 and W4 Mean Apache II score of 6.2: mild patients Limited to patients whose condition improved at D3 Localized peritonitis (50% of appendicitis cases) with surgery

Table 12 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Statistics	Comments
Montravers P 2016 [102]	Postoperative peritonitis following infection source control	Multicenter randomized (ratio 1/1) open-label study Empirical antibiotic therapy tailored to isolated bacteria	Treatment: 15 days	Treatment: 8 days	116/120	Days without antibiotics at D28: 15 vs. 12 ($P = 0.001$) Mortality: 10.3% vs. 6.7% ($P = 0.3$) New procedure at D28: 20% vs. 21% ($P = 0.84$) Length of stay in the ICU: 12 vs. 13 days ($P = 0.3$) Hospital length of stay: 30 vs. 30.5 days ($P = 0.94$) MDRB emergence (clinical and colonization) at D45: 55% vs. 58% ($P = 0.35$)	No differences in terms of outcome and complication occurrence between both groups	Empirical antibiotic therapy tailored to the bacteria isolated during surgery Severe ICU patients (SAPS II 45)
Chabok A 2012 [106]	Uncomplicated diverticulitis	Randomized study	IV and then oral antibiotic therapy for at least 7 days	No antibiotic therapy	314/309	Similar rate of hospital readmission for relapse at 1 year: 16% ($P = 0.881$)	No differences between both groups Same complication rates during hospital stay (1.9% vs. 1.0%; $P = 0.302$). Hospital length of stay: median of 3 days in both groups	
Schug-Pass C 2010 [128]	Uncomplicated diverticulitis	Randomized multicenter study	Ertapenem 4 days	Ertapenem 7 days	106	Full recovery at 1 month: 94.0% vs. 96.2%	No differences between both groups Shorter hospital length of stay: 7.8 ± 2.8 versus 9.7 ± 3.2 days; $P = 0.002$	Ertapenem study
Alonso S 2010 [129]	Uncomplicated diverticulitis	Non-randomized study	Oral amox-clav or oral ciprofloxacin/metronidazole, 7 days	–	70	Improvement at D4 and D7: 97%		Outpatient treatment possible for 70/96 (73%)
Hjern F 2007 [130]	Hospitalized diverticulitis without surgery	Monocentric retrospective study	IV and then oral antibiotic therapy Duration: 10-14 days	No antibiotic therapy	118/193	Treatment failure: 3 (3%) vs. 7 (4%) Mean follow-up of 30 months: relapse or surgery (33 [29%] vs. 53 [28%], $P = 0.97$)	No differences between both groups	Retrospective Non-comparable groups: higher proportion of severe signs in the antibiotic therapy group

Table 12 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Statistics	Comments
Runyon BA 1991 [108]	Ascitic fluid infection (AFI)	Randomized monocentric study	Cefotaxime 5 days	Cefotaxime 10 days	43/47	Attributable mortality (0% vs. 4.3%), hospital mortality (32.6% vs. 42.5%), microbiological eradication (93.1% vs. 91.2%), relapse/recurrence of AFI (11.6% vs. 12.8%)	No differences between both groups	1991 study
Regimbeau JM 2014 [113]	Acute calculous cholecystitis, with surgery	Randomized multicenter study	Amox-clav before and during surgery	Amox-clav before, during, and after surgery: 5 days	207/207	SSIs and other postoperative infections at 4 weeks: 35 (17%) vs. 31 (15%) Similar rates of complication following surgery	No differences between both groups	Grade I or II calculous cholecystitis, <5-day history, with surgery
Mazeh H 2012 [116]	Hospitalized acute calculous cholecystitis, without surgery	Randomized monocentric study	Amox-clav until hospital discharge	No antibiotic therapy	42/42	Similar hospital stay (3.8 vs. 3.9 days; $P = 0.89$) Similar rates of percutaneous drainage (5 vs. 12%, $P = 0.43$) and readmission to hospital (13 vs. 19%, $P = 0.73$) Delayed surgery: 62% vs. 86% ($P = 0.02$)	No differences between both groups	Only grade I calculous cholecystitis Non-antibiotic therapy group: strategy failure (8/42; 19%)
Lau WY 1990 [114]	Acute calculous cholecystitis, with surgery	Randomized monocentric study	Cefamandole before surgery, and then at H6 and H12	Cefamandole before surgery, and then for 7 days after surgery	100/103	SSI 7% vs. 5.8% Infusion-related thrombophlebitis: 6% vs. 16.5% ($P < 0.05$) Hospital length of stay: 7.2 vs. 8.9 days ($P < 0.05$)	Higher rate of complications with long-term treatment	No obstacle on the main biliary pathway before surgery Outcome assessment < 7 days
Van Lent A 2002 [118]	Cholangitis with ERCP drainage	Monocentric retrospective study	Post-ERCP antibiotic therapy	–	80	Median antibiotic therapy duration: 3 days Relapse unrelated to treatment duration (11/41 if ≤ 3 days, 4/19 if 3–5 days, 4/20 if > 5 days) No complication post-ERCP	No differences between the 3 groups	46% of bacteremia cases Successful ERCP during procedure (endoscopic observation) Sclerosing cholangitis and liver transplant were excluded

Table 12 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	*n*	Results	Statistics	Comments
Kogure H, 2011 [117]	Cholangitis with ERCP drainage	Monocentric prospective study	Antibiotic therapy discontinuation following ERCP in the absence of fever	–	18	Median apyrexia: 2 days (1–6) Median antibiotic therapy duration: 3 days (2–7)	No relapse in the 3 days following antibiotic therapy discontinuation	33% of bacteremia cases Many exclusion criteria (sclerosing cholangitis, chemotherapy, severity, etc.) 20 included (2 non-evaluable) out of 117 assessed for eligibility
Bennish LM, 1992 [122]	Shigellosis	Randomized monocentric study	Ciprofloxacin 1 or 2 doses	Ciprofloxacin 5 days	40/43/35	Clinical failure: 4/40 vs. 2/43 vs. 0/35 ($P = 0.12$ and > 0.2)	No differences between the 3 groups	Treatment failures were more frequent with type 1 *Shigella dysenteriae* and with the single-dose treatment vs. 5-day treatment (4/10 vs. 0/15, $P = 0.017$)
DuPont HL, 1992 [120]	Travelers' diarrhea	Randomized monocentric study	Ofloxacin 3 days	Ofloxacin 5 days	81/66	Clinical failure 77/81 (95%) vs. 59/66 (89%)	No differences between both groups, efficacy > placebo (56/79, 71%; $P = 0.0001$)	
Gotuzzo E 1989 [131]	Shigellosis	Randomized monocentric study	Co-trimoxazole 5 days	Norfloxacin single-dose	26/29	Disease duration: 2.5 days vs. 2 days ($P = 0.200$)	No differences between both groups	Similar microbiological failure: 1/24 vs. 0/25
Tribble DR 2007 [121]	Travelers' diarrhea	Bicentric randomized study	Azithromycin 1 dose	Azithromycin 3 days or levofloxacin 3 days	52/51/53	Clinical recovery at D3: 96% vs. 85% vs. 70%	No differences between the single-dose of azithromycin vs. the 3-day treatment but superior to levofloxacin ($P = 0.01$)	Predominance of *Campylobacter* spp. (64%). Microbiological eradication: 96% vs. 100% vs. 38% ($P = 0.01$)
Chinh NT 2000 [124]	Typhoid fever	Randomized monocentric study	Ofloxacin 5 days	Azithromycin 5 days	44/44	Clinical recovery at the end of treatment: 86.4% vs. 95.5%	No differences between both groups	Complicated presentations were excluded Longer time to apyrexia in the ofloxacin group Higher microbiological eradication with azithromycin for nalidixic acid-resistant strains
Frenck RW 2004 [125]	Typhoid fever	Randomized monocentric study	Ceftriaxone 5 days	Azithromycin 5 days	36/32	Clinical recovery at D7 (97 vs. 94%) and at D30 (81 vs. 100%)	No difference between both groups	Complicated presentations were excluded Lower rate of bacteremia clearance at D3 with azithromycin (62 vs. 100%, $P < 0.001$) More relapses with ceftriaxone (0 vs. 14%, $P < 0.05$)

IAI: intra-abdominal infection; SSI: surgical site infection; MDRB: multidrug-resistant bacteria; SAPS: simplified acute physiology score; amox-clav: amoxicillin–clavulanic acid; ERCP: endoscopic retrograde cholangiopancreatography; ICU: intensive care unit; IV: intravenous.

9.5.3. Complicated diverticulitis without surgery

We cannot recommend treatment durations as literature data is lacking. This type of diverticulitis is quite common and physicians often prescribe prolonged antibiotic therapies (15 days). A study comparing 7 vs. 15 days of treatment would be needed to validate a short treatment duration.

9.6. Ascitic fluid infection in cirrhosis patients: 5 days if community-acquired infection and antibiotic therapy with cefotaxime

A former study [108] evaluating cefotaxime showed that a 5-day treatment was not inferior to a 10-day treatment in terms of mortality, microbiological eradication, and relapse. This treatment duration is also recommended by experts [109–112]. However, the evolution of microbial epidemiology over the past 20 years must lead to new clinical trials aiming at validating treatment choices and durations.

Antibiotic therapy effectiveness must be reassessed with a new microbiological evaluation performed at 48 hours.

9.7. Cholangitis, cholecystitis

9.7.1. Mild cholecystitis with early surgery (< 72 hours): ≤ 24 hours of antibiotic therapy

The authors of a convincing study showed that antibiotics administered during surgery were equivalent to a 5-day postoperative treatment [113]. These results support those reported in Lau's study [114].

9.7.2. Cholecystitis without surgery

The IDSA [97] does not recommend any specific treatment duration, but antibiotics are always indicated, except for grade I cholecystitis [115]. Indeed, results from a randomized study of patients presenting with grade I cholecystitis who did not undergo surgery did not show the benefit of the antibiotic therapy [116]. Except for grade I cholecystitis, the absence of studies prevents us from suggesting a specific treatment duration. Considering the high frequency of this infection, a study comparing two antibiotic therapy durations would be needed.

9.7.3. Cholangitis: 3-day antibiotic therapy in case of successful drainage

Treatment relies on biliary drainage. Its efficacy is confirmed by endoscopy and by the absence of fever; following drainage, the antibiotic therapy can thus be reduced to 3 days (no benefit with a duration > 3 days, including in case of associated bacteremia) [117]. This short treatment duration has not been assessed in patients presenting with primary sclerosing cholangitis nor has it been studied in liver transplant recipients [118].

9.8. Acute diarrhea: 3-day treatment duration

When antibiotic therapy is indicated, the suggested treatment duration ranges from 3 to 5 days [119]. However, findings from a study of patients presenting with travelers' diarrhea – half of which were confirmed by stool cultures (mainly *Shigella* and enterotoxigenic *Escherichia coli*) – showed that a 3-day treatment with fluoroquinolones was as effective as a 5-day treatment. [120]. A single-dose azithromycin treatment also proved equivalent to a 3-day treatment, and this agent demonstrated its superiority versus 3 days of levofloxacin in patients traveling back from Thailand and presenting with diarrhea (64% of *Campylobacter*) [121]. The inferiority of the single-dose ciprofloxacin treatment must, however, be highlighted compared with a 5-day treatment in *S. dysenteriae* serotype 1 infection [122].

9.9. Typhoid fever

Treatment duration for typhoid fever ranges from 3 to 14 days depending on the agent used [123]. No comparison of treatment durations of a single agent has been performed. The authors of a study showed the efficacy of ofloxacin when administered for 5 days [124], but the emergence of resistance observed in several countries now restricts the use of this agent. Most experts thus recommend a 7-day treatment. More recently, a 5-day treatment with azithromycin has proved as effective as comparators (ceftriaxone [125] or ofloxacin [123]). The administration of a 5-day azithromycin treatment is thus considered an alternative, especially when confronted with fluoroquinolone resistance [126].

9.10. Clostridium difficile infections: 10-day treatment duration

This treatment duration is suggested in the latest European guidelines [127].

The main characteristics of study considered in this analysis are presented in Table 12.

9.11. Conclusions

Analyzing literature data helps in describing many of the infections mentioned above, for which one may suggest short treatments and prescribe treatment durations corresponding to the lower end of ranges mentioned in many guidelines. However, specific treatment durations cannot be suggested for cholecystitis without surgery and complicated diverticulitis without surgery. Both infections are probably a frequent cause of antibiotic misuse, and would justify the conduct of studies comparing two antibiotic therapy durations.

10. Urinary tract infections

Method.– Source: 2014 French guidelines on the management of community-acquired urinary tract infections [132], 2015 French guidelines on the management of healthcare-associated urinary tract infections [133], and American guidelines when available. The literature analysis conducted on PubMed from 2014 to 2015 did not show any new data.

Suggested treatment durations:

- 1 day (single-dose): acute uncomplicated cystitis (fosfomycin-trometamol);
- 3 days: catheter-related acute cystitis;
- 5 days:
  - acute uncomplicated cystitis (pivmecillinam or nitrofurantoin),
  - acute cystitis at risk of complications or healthcare-associated acute cystitis (co-trimoxazole or fluoroquinolones);
- 7 days:
  - acute cystitis at risk of complications or healthcare-associated acute cystitis (antibiotics other than co-trimoxazole or fluoroquinolones),
  - acute pyelonephritis (fluoroquinolone or injectable beta-lactam);
- 10 days: severe acute pyelonephritis and/or at risk of complications and/or healthcare-associated and/or antibiotics other than fluoroquinolone or injectable beta-lactam;
- 14 days: community-acquired or healthcare-associated male urinary tract infection (co-trimoxazole or fluoroquinolone).

10.1. Cystitis

10.1.1. Acute uncomplicated cystitis

- Single-dose of fosfomycin-trometamol.
- 5 days if pivmecillinam or nitrofurantoin.

For pivmecillinam, the IDSA recommends 3 to 7 days of treatment for uncomplicated cystitis. Nicolle performed a study [134] in 2002 of female patients aged between 18 and 65 years presenting with acute uncomplicated cystitis, and observed that the clinical recovery rate on Day 4 and Day 11 for patients treated with pivmecillinam for 3 days (483 patients) was 95% and 82%, respectively. This short treatment therefore seems to be an interesting alternative.

No study results are available to suggest a short treatment with nitrofurantoin.

Co-trimoxazole and fluoroquinolones were recommended in the IDSA guidelines as they allow for 3-day treatments. They are, however, not recommended in the French guidelines on the management of acute uncomplicated cystitis as they should be spared for more severe infections. Kavatha [135] and Gupta [136] performed studies including a total of 70 and 148 female patients, respectively. They respectively observed an efficacy rate of 100% and 90% with co-trimoxazole 160/800 mg, twice daily for 3 days.

10.1.2. Cystitis at risk of complications

- 5 days with co-trimoxazole or fluoroquinolone.
- 7 days with other agents (amoxicillin, pivmecillinam, nitrofurantoin, combination of amoxicillin/clavulanic acid, cefixime).

We are currently lacking study data supporting the use of shorter durations.

10.1.3. Healthcare-associated cystitis

- 3 days if symptoms improve following urinary catheter removal in female patients under 75 years of age and in the absence of frailty criteria.
- 5 days with co-trimoxazole or fluoroquinolone.
- 7 days with other agents (amoxicillin, pivmecillinam, nitrofurantoin, combination of amoxicillin/clavulanic acid, cefixime).

However, the authors of a study performed in 1991 [137] observed a similar success rate with a single-dose of co-trimoxazole and with a 10-day treatment in female patients presenting with lower urinary tract infection following catheter removal. Results from this small sample size study (27 female patients) would need to be confirmed.

For neurogenic bladder infections, asymptomatic urinary tract colonization and infection (no treatment required) need to be differentiated from symptomatic urinary tract infection, bearing in mind that these patients present with few symptoms.

With regard to intermittent catheterization, Mohler et al. [138] observed that a microbiologically tailored 10-day antibiotic therapy did not prove more effective than a 3-day treatment. Considering the small sample size (29 patients in each group) and the early publication of this work, this data would need to be confirmed. Dow performed a double-blind randomized placebo-controlled study in 2004 [139] and observed opposite results. The authors of this study evaluated catheter-associated urinary tract infections in paraplegic patients treated with ciprofloxacin for 3 or 14 days. Relapses were more frequent with the short treatment, and long-term sterilization was better in the long-term treatment group. It should, however, be noted that this study does not differentiate male from female urinary tract infections.

10.2. Pyelonephritis

The presence of bacteremia associated with urinary tract infection does not extend treatment duration.

10.2.1. Acute uncomplicated pyelonephritis

- 7 days with injectable beta-lactams or fluoroquinolones.
- 10 to 14 days otherwise.
- Treatment duration ranges from 5 to 7 days for aminoglycoside-based monotherapy.

The 2010 IDSA guidelines [140] recommend using levofloxacin 750 mg once daily for 5 days in female patients presenting with a mild infection. This recommendation is based on the study performed by Peterson et al. [141]. They compared

a 5-day single daily dose treatment with levofloxacin 750 mg versus ciprofloxacin treatment (IV 400 mg/oral 500 mg) twice daily for 10 days, and observed a similar efficacy on a large cohort of 1109 female patients. The study was, however, made of a mixed population of patients with 71.5% (782) of complicated urinary tract infection patients and only 28.5% (311) of pyelonephritis patients. Besides, a study conducted by Talan et al. showed that the ciprofloxacin single-dose was equivalent to a twice daily intake in this indication [142].

10.2.2. Acute pyelonephritis at risk of complications and severe acute pyelonephritis

- 10 to 14 days. Current guidelines suggest a 10- to 14-day treatment duration that should be modified on a case-by-case basis. No data is currently available to better define treatment duration. A longer treatment duration may be discussed for patients presenting with renal abscess for instance.

10.2.3. Healthcare-associated pyelonephritis

- 10 days.

10.3. Male urinary tract infections

- 14 days (minimum) with fluoroquinolone or co-trimoxazole or for healthcare-associated male urinary tract infections.
- 21 days with any other agent or for uropathy or severe immunodeficiency.

Ulleryd et al. [143] observed that two weeks and four weeks of treatment with ciprofloxacin were equivalent in febrile male urinary tract infection.

A randomized study (Prostashort) comparing two treatment durations (7 days versus 14 days) in non-nosocomial acute prostatitis caused by susceptible bacteria to fluoroquinolones is currently ongoing in France.

10.4. Studies to consider

Recent guidelines on chronic prostatitis management are lacking. A study of acute uncomplicated cystitis evaluating pivmecillinam for 3 days, or even nitrofurantoin, would be interesting. A study aiming to reduce treatment duration of symptomatic catheter-associated urinary tract infections in female patients over 75 years of age and/or presenting with frailty criteria would also be interesting.

The main characteristics of studies considered in this analysis are presented in Table 13.

11. Upper reproductive tract infections and sexually transmitted infections

Method:

- Guidelines:
  - Update. Empirical antibiotic therapy of uncomplicated urethritis and cervicitis, ANSM, October 2008 update [145],
  - French National Authority for Health (French acronym HAS). Uncomplicated urethritis and cervicitis: diagnostic and therapeutic strategies, 2015 [146],
  - 2015 CDC Guidelines: Sexually Transmitted Treatment Guidelines, 2015 [147],
  - 2012 Clinical Practice Guidelines of the French national association of gynecologists and obstetricians [148],
  - 2012 European guidelines: European guidelines for the management of pelvic inflammatory disease [149];
- PubMed search:
  - pelvic inflammatory disease and clinical review,
  - pelvic inflammatory disease and antibiotic therapy,
  - pelvic inflammatory disease and antibiotic and randomized;
- Definitions: guidelines approach the treatment of reproductive tract infections distinguishing uncomplicated urethritis and cervicitis from upper reproductive tract infections (URTIs), for which the following distinctions apply:
  - uncomplicated URTIs: endometritis and salpingitis usually requiring an outpatient management,
  - complicated URTIs: tubo-ovarian abscess, pelviperitonitis from pelvic origin.

Suggested treatment durations:

- single-dose:
  - urethritis and cervicitis (IM ceftriaxone 500 mg + oral azithromycin 1 g);
- 10 days:
  - uncomplicated upper reproductive tract infections (alternative: single-dose of IM ceftriaxone 500 mg + oral azithromycin 1 g, two intakes 7 days apart);
- 14 days:
  - complicated upper reproductive tract infections (tubo-ovarian abscess, pelviperitonitis).

11.1. Guidelines

The 2008 French guidelines on the management of urethritis and cervicitis, recently updated, and the 2015 update of the CDC (Center for Disease Control and Prevention) guidelines both favor the single-dose treatment combining an antibiotic active against *Neisseria gonorrhoeae* (IM ceftriaxone in first-line, IM spectinomycin or oral cefixime as a single-dose in 2nd and 3rd lines) and an anti-*Chlamydia* treatment (single-dose of azithromycin or doxycycline for 7 days) [145–147]. The CDC guidelines favor the azithromycin-based dual combination therapy for three reasons: better compliance, lower prevalence of *Neisseria gonorrhoeae* resistance to azithromycin, and potential synergistic effect of the combination [147].

The French, European, and Northern American guidelines on URTIs recommend a 14-day treatment duration

Table 13
References – urinary tract infections.
Bibliographie – infections urinaires.

Reference	Infection	Method	Study treatment	Comparator	Sample size	Results	Comments
Nicolle 2002 [134]	Acute cystitis	Randomized double-blind study	Pivmecillinam 400 mg twice daily for 3 days	Norfloxacin 400 mg twice daily for 3 days	955 female patients	Clinical recovery at the end of treatment: 95% vs. 96%, at 11 days: 82% vs. 88% (NS)	
Harding 1991 [137]	HR-UTI	Randomized study	Single-dose of co-trimoxazole	Co-trimoxazole 10 days	14/13	Eradication: 79% vs. 81%	Catheter-related UTI persisting after catheter removal Small sample size
Mohler 1987[138]	Neurogenic bladder infection		10 days of tailored antibiotic therapy	3 days of tailored antibiotic therapy	29/29	No difference (recovery, failure)	
Dow 2004 [139]	Moderate catheter-related UTI in paraplegic patients	Randomized Double-blind Placebo-controlled study	14 days of ciprofloxacin, 250 mg twice daily	3 days of ciprofloxacin, 250 mg twice daily	60	Relapses were more frequent with a short treatment Better long-term sterilization in the long-term treatment group	
Peterson 2008 [141]	APN or complicated UTI	Randomized double-blind study	Levofloxacin, 750 mg once daily for 5 days	Ciprofloxacin, 400/500 mg twice daily for 10 days	1109 including 782 complicated UTIs and 311 APNs	Out of 619 Bacterial eradication: 79.8% vs. 77.5% 95% CI [−8.8–4.1%]	
Talan 2004 [142]	APN or complicated UTI	Randomized double-blind study	Ciprofloxacin, 1000 mg once daily for 7 to 14 days	Ciprofloxacin, 500 mg twice daily for 7 to 14 days	1035, including 435 confirmed cases (343 complicated UTIs, 92 APNs)	Eradication: 89% vs. 85% (95% CI: −2.4%–10.3%) Clinical recovery 97% vs. 94% (95% CI: −1.2%–6.9%)	
Ulleryd 2003 [143]	Febrile UTI Male	Randomized 1-year follow-up	Ciprofloxacin 500 mg twice daily 2 weeks	Ciprofloxacin 500 mg twice daily 4 weeks	72	Clinical + bacteriological success at 14 days: 89% vs. 97%, NS	
Eliakim-Raz 2013 [144]	APN or febrile UTI	Meta-analysis	Treatment < 7 days	Treatment > 7 days		Clinical failure at the end of long-term treatment: RR 0.63 [95% CI: 0.33–1.18]	Similar results for fluoroquinolones and bacteremia subgroups
Kavatha 2003 [135]	Uncomplicated cystitis	Randomized	Co-trimoxazole 3 days	Cefpodoxime 3 days	70	Early clinical success: 100% vs. 98.4%	
Gupta 2007 [136]	Uncomplicated cystitis	Randomized study	Co-trimoxazole 3 days	Nitrofurantoin 3 days	148	Early clinical success: 90% vs. 90%	

UTI: urinary tract infection; HR-UTI: healthcare-related urinary tract infection; APN: acute pyelonephritis.

for complicated and uncomplicated presentations [147–149]. French guidelines suggest a treatment duration ranging from 14 to 21 days for complicated URTIs. European guidelines suggest, in the core text, a 10- to 14-day treatment for URTIs, but this duration is not mentioned in the tables.

A single IM dose of ceftriaxone is recommended in combination with doxycycline and metronidazole for 14 days in uncomplicated URTIs. A treatment regimen with a single-dose of ceftriaxone combined with azithromycin 1 g/week for 14 days is suggested in the French and European guidelines on uncomplicated URTIs.

None of these guidelines suggest tailoring antibiotic therapy duration to the performance of drainage and its efficacy for complicated URTIs.

11.2. Randomized studies

A summary of randomized studies published on the use of antibiotic therapies in URTIs is available in Table 1.

A total of 10 randomized studies have been published since 1993 [150–159]. None of them aimed to compare a conventional treatment duration with a shorter one.

Most studies compared treatments administered for 14 days in both groups. Patients enrolled in some treatment groups received a combination containing a single-dose of ceftriaxone or ciprofloxacin and a 14-day treatment with doxycycline ± metronidazole.

Martens et al. compared two treatment groups receiving treatment for 10 days, and observed good efficacy (93%) in the cefoxitin + doxycycline group, which is suggested in several guidelines [150]. Hemsell et al. compared two treatment groups receiving treatment for 2 to 10 days [153]. Guidelines do not mention the combination of meropenem and clindamycin with gentamicin. Bevan et al. compared the administration of azithromycin alone or in combination with metronidazole for 6 to 8 days, and observed more than 95% efficacy in both groups [154]. Finally, Savaris et al. highlighted the efficacy (98%) of a single-dose of ceftriaxone combined with azithromycin 1 g once a week for 2 weeks [156]. Only the latter combination therapy with azithromycin is mentioned in the French and European guidelines.

11.3. Limitations and perspectives

Most published studies evaluated treatment regimens before the progression of *Neisseria gonorrhoeae* resistance, especially to fluoroquinolones. Recent data seems to point to the responsibility of *Mycoplasma genitalium* and the emerging resistance to tetracyclines and macrolides [160].

Very few of these studies focused on evaluating treatment regimens for complicated URTIs. Considering the absence of data, it seems difficult to suggest treatment regimens shorter than 14 days. Similarly, the administration of a single-dose treatment for complicated URTIs, such as *Neisseria gonorrhoeae* pelviperitonitis, has not been studied. Studies are needed to compare 7 versus 14 days of treatment, stratified on the performance of drainage, with agents of compatible susceptibility profiles in the treatment of infections due to the most frequent bacteria.

Studies evaluating shorter treatment durations in uncomplicated URTIs are also needed (single-dose of ceftriaxone, single weekly dose over 15 days, or 4–5 days of azithromycin). These studies should be based on molecular biology assays identifying bacteria instead of broad treatment for all possible bacteria.

Finally, all published studies used the same endpoint, i.e. short-term clinical recovery. This criteria does not necessarily seem to be predictive of long-term complications such as infertility [161]. However, studies evaluating this endpoint do not appear feasible for now.

The main characteristics of studies considered in this analysis are presented in Table 14.

12. Bone and joint infections

Method: review of current guidelines issued by the main scientific societies (IDSA, BSAC, SPILF, ESCMID) and literature analysis on PubMed (analysis of articles published over the past 20 years) using the following search terms: “prosthetic joint infection”, “orthopedic implant-related infection”, “prosthetic hip or knee associated infections”, “septic arthritis”, “infectious spondylodiscitis”, “diabetic foot osteomyelitis”, “osteomyelitis”, “antibiotic therapy”, “antimicrobial agent”, “short versus long-term”, “weeks”, “months”, and “duration”. We also analyzed the abstracts of the last two years’ Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and European Congress of Clinical Microbiology and Infectious Diseases (ECCMID).

Suggested treatment duration:

- 6 weeks:
  - prosthetic joint infections (the management of complex case patients must be discussed with the reference center for complex bone and joint infections),
  - spondylodiscitis (except for osteosynthesis device),
  - diabetic foot osteomyelitis without surgery.

12.1. Prosthetic joint infections (PJIs)

Specific algorithms were designed to determine surgical treatment, as it is a crucial component of the therapeutic strategy [162]. Suggested treatments range from debridement-lavage without prosthesis removal, through one-step or two-step prosthesis replacement (with or without antibiotic-coated intra-articular device), to bone resection. Treatment choice is mainly based on symptom duration, prosthesis and surrounding tissue state, results of the preoperative synovial fluid culture if performed, and on susceptibility of responsible bacteria to anti-infective agents.

However, although surgical treatments are rather well-codified, the duration of the associated antibiotic therapy remains unclear. In 2010, the SPILF recommended antibiotic therapy durations ranging from 6 to 12 weeks [163]. The 2013 IDSA [164] guidelines recommend administering treatment for 3 to 6 months, including 2 to 6 weeks of intravenous treatment for staphylococcal PJIs without prosthesis removal (debridement-lavage or one-step prosthesis replacement), and only 4 to 6 weeks of oral or intravenous treatment for infections caused by other bacteria and for other situations. Recent international guidelines [165,166] mentioned the same treatment durations, without making any distinction between causative agents.

PJI diagnosis is confirmed when at least one of the following criteria is observed: growth of the same microorganism on at least two synovial fluid or periprosthetic tissue cultures, purulent aspect of the synovial fluid or at implantation site, acute inflammation observed at pathological examination of the periprosthetic tissue or presence of a fistula. Infections are classified as early (< 3 months after surgery), delayed (3 to 24 months), and late onset (> 24 months). Recovery is defined by the absence

Table 14
References – upper reproductive tract infections (URTI) and sexually transmitted infections.
Bibliographie – infections génitales hautes (IGH) et infections sexuellement transmises.

Reference	Infection	Method	Treatment group 1	Treatment group 2	Clinical efficacy	Microbiological efficacy
Martens 1993 [150]	Uncomplicated URTI	Randomized, multicenter, double-blind study	Oral ofloxacin Duration: 10 days $n = 128$	Intramuscular cefoxitin followed by oral doxycycline Duration: 10 days $n = 121$	95% vs. 93%	100% vs. 100% among *Neisseria gonorrhoeae* and *Chlamydia trachomatis*
Witte 1993 [151]	URTI confirmed by laparoscopy	Randomized, double-blind study	Oral doxycycline at D1 followed by oral metronidazole Duration: 10–14 days $n = 20$	Oral pefloxacin + metronidazole Duration: 10–14 days $n = 20$	35% vs. 45%	Not evaluated
Arredondo 1996 [152]	Uncomplicated URTI	Randomized, multicenter, double-blind study	Oral clindamycin + oral ciprofloxacin Duration: 14 days $n = 67$	Single intramuscular dose of ceftriaxone + oral doxycycline Duration: 14 days $n = 64$	97% vs. 95%	100% vs. 100% among *N. gonorrhoeae* and *C. trachomatis*
Hemsell 1997 [153]	URTI	Randomized multicenter study	IV meropenem Duration: 2–10 days $n = 211$	Clindamycin + IV gentamicin Duration: 2–10 days $n = 184$	88% vs. 90%	88% vs. 86% among *N. gonorrhoeae* *C. trachomatis* and anaerobes
Bevan 2003 [154]	URTI	Randomized study	IV azithromycin for 1–2 days, then oral route for 5–6 days Duration: 6–8 days $n = 102$	IV azithromycin for 1–2 days, then oral route for 5–6 days + IV metronidazole for 1–2 days, then oral route for 10–11 days Duration: 11–12 days $n = 105$	97% vs. 96%	100% vs. 100% among *N. gonorrhoeae* strains 100% vs. 96% among *C. trachomatis* strains 83% vs. 83% among *Mycoplasma hominis* strains 100% vs. 100% among anaerobes
Ross 2006 [155]	Uncomplicated URTI	Non-inferiority, randomized, multicenter, double-blind study	Oral moxifloxacin Duration: 14 days $n = 275$	Oral ofloxacin + oral metronidazole Duration: 14 days $n = 289$	90% vs. 91%	100% vs. 82% among *N. gonorrhoeae* strains 89% vs. 86% among *C. trachomatis* strains
Savaris 2007 [156]	Uncomplicated URTI	Randomized, equivalence study	Single-dose of ceftriaxone + azithromycin 1 g once a week for 14 days Duration: 14 days $n = 53$	Single-dose of ceftriaxone + oral doxycycline for 14 days Duration: 14 days $n = 53$	98% vs. 86%	Not evaluated
Heystek 2009 [157]	Uncomplicated URTI	Non-inferiority, randomized, multicenter, double-blind study	Oral moxifloxacin Duration: 14 days $n = 177$	Single oral dose of ciprofloxacin + oral doxycycline and oral metronidazole for 14 days Duration: 14 days $n = 161$	97% vs. 98%	Not evaluated
Judlin, 2010 [158]	Uncomplicated URTI	Non-inferiority, randomized, multicenter double-blind study	Oral moxifloxacin Duration: 14 days $n = 130$	Oral levofloxacin + oral metronidazole Duration: 14 days $n = 130$	78% vs. 82%	Overall eradication rate: 90% vs. 85%
Asicioglu, 2013 [159]	Uncomplicated URTI	Randomized, multicenter study	Oral moxifloxacin Duration: 14 days $n = 560$	Oral ofloxacin + oral metronidazole Duration: 14 days $n = 543$	79.5% vs. 83%	Overall eradication rate: 83% vs. 84.5%

URTI: upper reproductive tract infection; IM: intramuscular; IV: intravenous.

of clinical signs of infection, a normal C-reactive protein (CRP) rate, and the absence of radiological signs of bone destruction or infection following an average follow-up of two years. Treatment failure is defined as persistent clinical and/or biological signs of infection, or as a new microbiological isolation of the causative agent.

A total of 17 studies have been reviewed and are presented in Table 15. The overall number of patients is 1214, with a sex ratio of 1/1. Most infections were early onset infections with a short duration of symptoms. *Staphylococcus aureus* was responsible for approximately two-thirds of infections.

Only two studies were prospective and randomized, but with a relatively small sample size [167,168]. Five studies were prospective but non-randomized [169–173], and the other ones were retrospective. Only 6 studies out of 17 enrolled more than 100 patients [169,172–176] and some of them were monocentric. Patient types also varied substantially. Another limitation lies in the lack of variety of antibiotic treatments used. Most studies used oral antibiotic treatments as a combination of fluoroquinolone and rifampicin, even though with few exceptions, such as the use of linezolid [177].

Ranges of antibiotic therapy duration are also quite limited, restricting the comparison to durations of 6 or 12 weeks and preventing the evaluation of treatment durations of 4 or 8 weeks. Antibiotic therapy brevity also depends on the surgical strategy. For instance, studies using debridement-lavage compared short treatments of 6, 7, or 8 weeks, but never less than that. Much shorter treatment durations have been evaluated in studies focusing on patients undergoing two-step prosthesis removal/reimplantation, especially with the use of antibiotic-coated spacer. Five studies thus evaluated treatment durations shorter than 6 weeks, some even evaluated a 1-week treatment [178–181] or no antibiotic therapy at all following surgery [175].

The success rates observed in these studies range from 71 to 92%. Although very few studies primarily aimed to compare treatment durations, some of them evaluated factors associated with treatment success or failure. The 2010 study of Bernard et al. did not report any variables significantly associated with recovery [169]. Brandt et al. observed that symptom duration > 2 days (RR 4.16 [1.67–10.39]) was the only variable associated with treatment failure in the multivariate analysis [182]. Laffer et al. observed, in their 2006 study, a significantly lower success rate for delayed onset infections ($P < 0.03$) [183]. Other studies also reported that multidrug-resistant staphylococcal infections were associated with poor prognosis (59.5% success rate vs. 73.6%) [176]. The need for a second debridement procedure (OR 20.4 [2.3–166.6] $P = 0.006$) and CRP > 22 mg/dl (OR 9.8 [1.5–62.5] $P = 0.01$) were both independently associated with treatment failure in Vilchez et al.'s study [184].

Despite these limitations, no study reported an association between prolonged antibiotic therapy duration and clinical success, or between short antibiotic therapy and risk of treatment failure (Table 15).

Rates of adverse effects and treatment costs were sometimes used as secondary endpoints. Hsieh et al. observed that 11% of patients included in the "prolonged antibiotic therapy" group presented with complications such as nephrotoxicity and neutropenia. Shorter treatments also helped in reducing hospital length of stay (from 43 to 18 days, $P < 0.001$) and direct medical cost (from $21,756 to $13,732, $P < 0.001$) [178].

Considering these results and despite the limitations of the studies reviewed, a 6-week antibiotic therapy may be recommended, regardless of the chosen surgical treatment. Large-scale randomized prospective studies are, however, needed to validate this treatment duration.

12.2. Bone and joint infections, excluding device-related infections (Table 16)

12.2.1. Diabetic foot osteomyelitis

The 2006 SPILF guidelines suggest a 4 to 6-week treatment when partial exeresis of infected tissues is performed and at least 6 weeks of treatment when surgical procedure is not performed [185].

The 2012 IDSA guidelines suggest the same treatment durations, and also suggest a 3-month or longer treatment for osteitis patients who did not undergo surgical exeresis [186]. A meta-analysis performed by Cochrane in 2013 did not report any controlled study enabling to determine the optimal treatment duration for chronic osteitis [187]. The results of a controlled study indicated that six weeks of treatment should be enough for chronic osteitis patients who did not undergo surgery [188].

Many studies evaluated various agents in the treatment of bone and joint infections, but sample size is usually small and the infection type definition often lacks in precision to enable a comparative analysis of treatment durations [189].

12.2.2. Septic arthritis

The last SPILF guidelines on the management of septic arthritis were published in 1990 [190]. The British Society for Antimicrobial Chemotherapy (BSAC) issued guidelines in 2006 and suggested administering a 6-week treatment [191]. Some authors suggest prescribing 4 to 6 weeks of treatment for < 10-day history of acute arthritis, and 6 to 12 weeks for > 10-day history of arthritis [192]. No controlled study has so far evaluated treatment durations. Retrospective cohort studies showed that a treatment administered for more than 6 weeks does not seem necessary [173]. Usual mortality rates were observed with 2- or 3-week treatments administered for streptococcal acute arthritis and 4- to 6-week treatments for staphylococcal infections [193]. Following successful lavage, a 14-day treatment – including 7 days of intravenous administration – may not be associated with an additional risk of recurrence according to the results of a monocentric retrospective study [194]. There is currently no strong evidence supporting the need for a change in current practices by reducing treatment duration.

12.2.3. Spondylodiscitis

The most recent French guidelines published in 2009 [195] recommend 6 to 12 weeks of treatment, but they do not mention which criteria should be applied to favor using the lower or upper end of this range. The authors of a retrospective cohort study published in 2007 [196] suggested that a 6-week treatment was enough.

Table 15
References – prosthetic joint infections.
Bibliographie – infections sur matériel prothétique ostéo-articulaire.

Type of surgical treatment	Antibiotic therapy duration (including IV route)	Number of patients	Microorganisms[b]	Success rate Short/long	Study type/evidence required	References
Hip						
Debridement-lavage	3 months (15 days)	33[a]	*Staphylococci* 100%	79.1%	Randomized double-blind prospective study	Zimmerli et al., 1998 [167]
	8 weeks vs. 3 months	21	*Staphylococci* 100%	91% vs. 94%/NS	Open-label randomized prospective multicenter study	Lora-Tamayo et al., 2013 [168]
	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	60[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Prospective monocentric study	Bernard et al., 2010 [169]
	3 months (3–7 days)	12	*Staphylococci* 22/29	82.7%	Prospective monocentric study	Berdal et al., 2005 [170]
	7 weeks	38	*Staphylococci* 17/38; *Streptococci* 2/38	71%	Prospective monocentric study	Westberg et al., 2012 [171]
	6 weeks vs. 12 weeks	123[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
	88 days (11 days)	18	*S. aureus* 100%	75.5%	Retrospective monocentric study	Vilchez et al., 2011 [184]
	2 months (4 weeks) vs. 3 months (4 weeks)	32	*Staphylococci* 91/132; *Streptococci* 29/132; Gram-negative bacilli 17/132	87.5% vs. 89.5%/NS	Retrospective monocentric study	Puhto et al., 2012 [174]
One-step prosthesis replacement	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	10[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Prospective monocentric study	Bernard et al., 2010 [169]
	12 weeks (4-6 weeks)	157	*Staphylococci* 84/157; *Streptococci* 24/157	94.9%	Prospective monocentric study	Zeller et al., 2014 [172]
	6 weeks vs. 12 weeks	20[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
Two-step prosthesis replacement	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	57[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Open-label prospective multicenter study	Bernard et al., 2010 [169]
	6 weeks vs. 12 weeks	96[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
	(1 week) vs. 6 weeks (4 weeks)[c]	99	*Staphylococci* 57/99; *Pseudomonas aeruginosa* 13/99	89% vs. 91%/NS	Retrospective monocentric study	Hsieh et al., 2009 [178]
	(5 days)[c]	31	*Staphylococci* 24/31; *Streptococci* 3/31; Enterococci 2/31	100%	Retrospective monocentric study	Mc Kenna et al., 2008 [179]
	(2 weeks)[c]	44	*Staphylococci* 32/44; Enterococci 6/44; *Streptococci* 5/44	92.7%	Retrospective monocentric study	Whittaker et al., 2009 [180]
	No associated antibiotic therapy	114	*Staphylococci* 70/114; Enterococci 14/114; *Streptococci* 4/114	87.7%	Retrospective monocentric study	Stockley et al., 2008 [175]
Non-specified	6 weeks	43[a]	*Staphylococci* 60/118; *Streptococci* 16/118	91.50%	Prospective monocentric study	Fahrad et al., 2010 [173]
	7.2 weeks (3–7 days)	15	*Staphylococci* 19/20	80%	Retrospective monocentric study	Bassetti et al., 2004 [177]

Table 15 (*Continued*)

Type of surgical treatment	Antibiotic therapy duration (including IV route)	Number of patients	Microorganisms[b]	Success rate Short/long	Study type/evidence required	References
Knee						
Debridement-lavage	6 months (15 days)	33[a]	*Staphylococci* 100%	79.10%	Randomized double-blind prospective study	Zimmerli et al., 1998 [167]
	8 weeks vs. 6 months	18	*Staphylococci* 100%	91% vs. 94%/NS	Open-label randomized prospective multicenter study	Lora-Tamayo et al., 2013 [168]
	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	60[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Prospective monocentric study	Bernard et al., 2010 [169]
	3 months (3–7 days)	6	*Staphylococci* 22/29	82.7%	Prospective monocentric study	Berdal et al., 2005 [170]
	6 weeks vs. 12 weeks	123[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
	3 months (4 weeks) vs. 6 months (4 weeks)	54	*Staphylococci* 91/132; *Streptococci* 29/132; Gram-negative bacilli 17/132	87.5% vs. 89.5%/NS	Retrospective multicenter study	Puhto et al., 2012 [174]
	88 days (11 days)	35	*S. aureus* 100%	75.5%	Retrospective monocentric study	Vilchez et al., 2011 [184]
	< 6 months (2 weeks) vs. > 6 months (2 weeks)	21	*Staphylococci* 25/40; *Streptococci* 5/40	91% vs. 87%/NS	Retrospective monocentric study	Laffer et al., 2006 [183]
One-step prosthesis replacement	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	10[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Prospective monocentric study	Bernard et al., 2010 [169]
	6 weeks vs. 12 weeks	20[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
	< 6 months (2 weeks) vs. > 6 months (2 weeks)	2	*Staphylococci* 25/40; *Streptococci* 5/40	91% vs. 87%/NS	Retrospective monocentric study	Laffer et al., 2006 [183]
Two-step prosthesis replacement	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	57[a]	*Staphylococci* 84/144; *Streptococci* 31/144	80%/NS	Prospective monocentric study	Bernard et al., 2010 [169]
	6 weeks vs. 12 weeks	96[a]	MRSA 42/307	74.9% vs. 71.6%/NS	Retrospective multicenter study	Chaussade et al., 2013 [176]
	< 6 weeks vs. > 6 weeks +[c]	37	*Staphylococci* 100%	87% vs. 91%/NS	Retrospective multicenter study	Mittal et al., 2007 [181]
	< 6 months (2 weeks) vs. > 6 months (2 weeks)	13	*Staphylococci* 25/40; *Streptococci* 5/40	91% vs. 87%/NS	Retrospective monocentric study	Laffer et al., 2006 [183]
Non-specified	6 weeks	43[a]	*Staphylococci* 60/118; *Streptococci* 16/118	91.50%	Prospective monocentric study	Fahrad et al., 2010 [173]
	7.2 weeks (3–7 days)	5	*Staphylococci* 19/20	80%	Retrospective monocentric study	Bassetti et al., 2004 [177]

IV: intravenous: MRSA: methicillin-resistant *S. aureus*; NS: non-significant.

[a] Hip and knee taken together.

[b] Comprising all types of arthroplasty and surgical treatments.

[c] Use of an antibiotic loader spacer.

Table 16
Treatment durations – bone and joint infections, except for device-related infections.
Durées de traitement – infections ostéo-articulaires hors infections sur matériel.

Type of infection	Duration of conventional treatment	Short treatment	Target population for short treatment	Evidence required for a short treatment	Comments
Septic arthritis	6 weeks	14 days after drainage	Well-documented infection following successful drainage	Retrospective (cohorts)	Insufficient to change practices
Diabetic foot osteomyelitis	>6 weeks in the absence of excision	6 weeks	All populations	Randomized study (2015)	Small sample size stressing the need for further studies
Spondylodiscitis	6 to 12 weeks	6 weeks	All populations	Randomized study (2015)	Justifying a change in practices

The first multicenter randomized controlled study was published in 2015 [197] and showed that a 6-week treatment was not inferior to 12 weeks. The 2015 IDSA guidelines recommend 6 weeks of treatment for all infection types [198].

The main characteristics of studies considered in this analysis are presented in Table 17.

13. Skin and soft tissue infections

Suggested treatment durations:

- 3 days: superficial skin infections (when antibiotics are indicated);
- 5 days: preemptive treatment for animal bites;
- 7 days: bacterial cellulitis, including erysipelas, wound infections, and extensive skin abscess (lesion > 75 cm^2).

Method.– We used the following search terms to perform the literature analysis: "skin and soft tissue infection" and "skin and skin structure infection". We only reviewed studies comparing two treatment groups and for which treatment durations were mentioned (even when treatment duration was not the primary endpoint). All bone and joint infections, confirmed or suspected, reported in these studies were excluded from the analysis.

This document does not focus on treatment duration for diabetic foot infections or necrotizing fasciitis.

Surgery, when it can be performed, helps in reducing the duration of antibiotic therapy and can even prevent it.

Other factors may influence treatment duration: the antibiotic choice (bactericidal/bacteriostatic, tissue concentration, half-life, etc.), the causative agent(s), vulnerability factors of the host (neutropenia, immunodeficiency, etc.).

We only found one randomized comparative study using treatment duration as primary endpoint [199].

The other studies compared two antibiotics with either similar or different treatment durations depending on treatment groups and comparators. They included heterogeneous populations of patients, infections of various severity, and used various clinical and/or microbiological endpoints; treatment duration interpretation was thus very difficult.

However, the Food and Drug Administration (FDA) has recently suggested standardizing infections and efficacy criteria [200]. "SSTIs" (skin and soft tissue infections) used to refer to bacterial infections of varying severity affecting the epidermis, dermis, or subcutaneous tissues, and "cSSTIs" (complicated skin and soft tissue infections) used to refer to these very same infections but with deep subcutaneous tissue involvement or the need for surgical treatment. The FDA now recommends using the term "ABSSSIs" (acute bacterial skin and skin structure infections) which refers to cellulitis, wound infections, and extensive skin abscesses (lesion > 75 cm^2). "cSSTIs" are included within these infections and refer to bedsore infections, venous or arterial ulcer infections, bite infections (animal or human), surgical site infections, and post-trauma infections. Burn-related infections and diabetic foot infections with or without osteitis are considered separately. These terms are used in the recapitulative table of publications on treatment durations of skin and soft tissue infections; almost all these studies use the terms "SSTIs", "cSSTIs", and "ABSSSIs".

The primary efficacy endpoint suggested by the FDA is the reduction of at least 20% in the lesion size at 48–72 hours. Lesion clearance 7 to 14 days after antibiotic therapy completion is suggested as secondary endpoint.

French guidelines on erysipelas and cellulitis were drafted 15 years ago [201]. American guidelines were more recently published on skin and soft tissue infections [202].

The summary table of this work (Table 18) suggests considering the following types of infections separately:

- superficial skin infections (impetigo, ecthyma, furuncles in patients with underlying conditions, anthrax);
- animal bites;
- bacterial cellulitis including erysipelas and infections falling under the term "ABSSSIs".

Table 17
References – bone and joint infections, except for device-related infections.
Bibliographie – infections ostéo-articulaires hors infection sur matériel.

Type of surgical treatment	Antibiotic therapy duration (including IV route)	Number of patients	Microorganisms	Success rate Short/long	Study type/Evidence required	References
Spondylodiscitis						
If required	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	351	*S. aureus* 145 (41%); CoNS 61 (17%); *Streptococci* 32 (18%)	90.9% vs. 90.9%	Randomized double-blind prospective multicenter study	Bernard et al., 2015 [197]
	6 weeks (3 weeks) vs. 6 weeks (4 weeks)	120		34 (94) vs. 75 (89)	Retrospective multicenter study	Roblot et al. 2007 [196]
Septic arthritis	3–4 weeks	32	*Streptococci* 32 (18%)	80%	Retrospective monocentric study	Nolla et al. 2015 [193]
	4–6 weeks	145	*S. aureus* 145 (41%)		Retrospective monocentric study	Nolla et al. 2015 [193]
	6 weeks	43	*Staphylococci* 60/118; *Streptococci* 16/118	91.5%	Prospective monocentric study	Fahrad et al., 2010 [173]
Diabetic foot osteomyelitis						
Drainage	2 weeks (1 week) vs. >4 weeks	169	*Staphylococci* 98 (52%)	NS*	Retrospective monocentric study	Uckay et al. 2011 [194]
Absence	6 weeks (2 weeks) vs. 12 weeks (2 weeks)	40	*Staphylococci* 20 (34%) Polymicrobial infection 18/40 (45%)	12/20 vs. 14/20 (65%)	Randomized prospective multicenter study	Tone et al. 2015 [188]

No study has so far been conducted on treatment duration for superficial skin infections. For instance, American guidelines suggest 7 days of treatment for impetigo and ecthyma [202]. These same guidelines recommend a 5-day treatment for erysipelas and other cellulitis infections, although mentioning that treatment duration may be prolonged if no improvement is observed after 5 days.

The 2000 French guidelines recommended 15 days of treatment for erysipelas; no treatment duration was, however, recommended for necrotizing cellulitis [201].

Only one randomized study comparing 5-day and 10-day levofloxacin treatments was performed. The authors concluded to the equivalent efficacy of both treatments [199]. However, the recent French update on fluoroquinolone stewardship mentions that this therapeutic class is not indicated in the treatment of skin and soft tissue infections, thus reducing the usefulness of this study that aimed to evaluate two treatment durations with the same antibiotic and showed the non-inferiority of the shorter 5-day treatment. As for the other studies analyzed in this review, their authors all concluded that a 7- to 10-day antibiotic therapy seemed enough [203–209].

The IDSA recommends a shorter treatment (5 days), with the possibility to further extend treatment in case of incomplete recovery on Day 5. They, however, do not give additional information [202].

Treatments of skin and soft tissue infections, even complicated ones, known as "(c)SSTIs (or (c)SSSIs)", and more recently of acute bacterial infections referred to as "ABSSSIs", have been evaluated for an average of 10 days with the oldest agents [199,204,206,207,210].

New agents could help in reducing treatment duration: 6 days for tedizolid [211,212], single-dose administration for oritavancin [66], or two administrations one week apart for dalbavancin [213,214]. However, these are not "true" short antibiotic therapies given the agents' very long half-life.

A Cochrane review suggests that the optimal duration of preemptive antibiotic therapy for animal bite is 5 days [215].

The main characteristics of studies considered in this analysis are presented in Table 18.

14. Febrile neutropenia

Method.– Source: IDSA guidelines on the management of febrile neutropenia [225], European ECIL-4 guidelines [226], and literature analysis on PubMed from 2013 to 2015.

Initiating a broad-spectrum antibiotic therapy is recommended to treat febrile neutropenia. Its duration is, however, disputed: American guidelines [225,226] make the distinction between several situations. When the infection is clinically and/or microbiologically documented, the antibiotic therapy must be continued at least until neutropenia correction (neutrophil count > 500 cells/mm^3), or even longer depending on the clinical situation. For fever of unknown origin (FUO), the antibiotic therapy should be continued at least until the end of the aplasia. The authors of a randomized study [227] compared antibiotic therapy discontinuation and antibiotic therapy

Table 18
References – skin and soft tissue infections.
Bibliographie – infections de la peau et des tissus mous.

Reference	Infection	Method	Treatment group 1	Treatment group 2	Number of patients included	Results	Comments
Hepburn 2004 [199]	ABSSI Cellulitis	Randomized double-blind study	Oral levofloxacin 500 mg/day, 10 days	Oral levofloxacin 500 mg/day, 5 days	Treatment group 1: 43 Treatment group 2: 44	Treatment duration: group 1: 10 days; group 2: 5 days Resolution on Day 14: group 1: 98%; group 2: 98%	
Bergkvist 1997 [203]	Erysipelas	Randomized study	Antibiotic + prednisolone	Antibiotic + placebo	Treatment group 1: 54 Treatment group 2: 54	Treatment duration = 8 days Median time to recovery: Day 5 for group 1; Day 6 for group 2 ($P < 0.01$)	
Bernard 1992 [204]	Erysipelas	Randomized study	Roxithromycin	Penicillin	Treatment group 1: 31 Treatment group 2: 38	Treatment duration = 10 days Treatment duration = 10 days after apyrexia in both groups Mean treatment duration: group 1: 13 days; group 2: 13 days Rate of recovery: group 1: 84%; group 2: 76% (NS)	
Dall 2005 [205]	Cellulitis	Pilot study	Only antibiotics (1st generation cephalosporin)	Antibiotic + ibuprofen	Treatment group 1: 33 Treatment group 2: 31	Treatment duration = 10 days in both groups (5 days of ibuprofen in group 2) Reduction of inflammation: group 1: 9% on Day 3: group 2: 82.8% on Day 2 ($P < 0.05\%$)	
Pallin 2013 [206]	Cellulitis	Randomized double-blind study	Cefalexin	Cefalexin + trimetho-prim/sulfamethoxazole	Treatment group 1: 73 Treatment group 2: 73	Treatment duration = 14 days Clinical recovery: group 1: 85%; group 2: 82% (NS)	
Aboltins 2015 [207]	Cellulitis	Randomized study	Oral cefalexin	IV cefazolin	Treatment group 1: 24 Treatment group 2: 23	Treatment duration = 10 days Stabilization of the inflammatory area: group 1: 1.29 days; group 2: 1.78 days Overall rate of clinical failures: group 1: 22%; group 2: 4% ($P = 0.10$)	
Breedt 2005 [208]	Skin and soft tissue infections (SSTIs)	Randomized double-blind study	Tigecycline	Vancomycin + aztreonam	Treatment group 1: 261 Treatment group 2: 259	Treatment duration: "until Day 14" for both groups Clinical response rate: group 1: 84.3%; group 2: 86.9%	
Chuang 2011 [209]	Complicated skin and skin structure infections (cSSSIs)	Randomized double-blind study	Tigecycline	Vancomycin + aztreonam	Treatment group 1: 63 Treatment group 2: 64	Treatment duration = 5 to 14 days in both groups Rates of recovery are not significantly different	Difficult interpretation study, including Indians and Taiwanese patients, various infections, and highly variable treatment durations

Table 18 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	Number of patients included	Results	Comments
Weigelt 2005 [216]	Complicated skin and soft tissue infections (cSSTIs)	Randomized open-label study	IV or oral linezolid (600 mg twice daily)	IV vancomycin (1 g twice daily)	Treatment group 1: 592 Treatment group 2: 588	Mean treatment duration: group 1 = 12 days; group 2 = 11 days Rate of recovery (test of cure/Intent-to-treat): group 1: 92.2%/75.3%; group 2: 88.5%/70.2% ($P = 0.057/0.0496$)	Infections = cellulitis, abscesses, infected ulcers, or burns
Itani 2010 [217]	Complicated skin and soft tissue infections (cSSTIs)		IV or oral linezolid (600 mg twice daily)	IV vancomycin (15 mg/kg twice daily)	Treatment group 1: 537 Treatment group 2: 515	Mean treatment duration: group 1 = 9 days; group 2 = 8 days Clinical success rate (Per protocol/Intent-to-treat): group 1: 84%/81%; group 2: 80%/74% ($P = 0.249/0.048$) Microbiological success rate (Per protocol): group 1: 75%; group 2: 68.4% ($P = 0.127$)	
Stevens 2000 [218]	Complicated skin and soft tissue infections (cSSTIs)	Randomized double-blind study	IV linezolid (600 mg twice daily), then switch to the oral route	IV oxacillin (2 g four times a day), then switch to the oral route (dicloxacillin)	Treatment group 1: 403 Treatment group 2: 423	Mean treatment duration: group 1: 13.4 days; group 2: 13.4 days Clinical recovery rate (Intent-to-treat/clinically assessable patients): group 1: 69.8%/88.6%; group 2: 64.9%/85.8%	Infections = major abscess, infected ulcer, major burn, or deep and extensive cellulitis
Moran 2014 [211]	Acute bacterial skin and skin structure infections (ABSSSIs)	Randomized double-blind study	Oral tedizolid 200 mg once daily 6 days	Oral linezolid 600 mg twice daily 10 days	Treatment group 1: 332 Treatment group 2: 334	Treatment duration: group 1: 6 days; group 2: 10 days Rate of early clinical response (at least 20% reduction in lesion size within 48–72 hours): group 1: 85%; group 2: 83% (NS)	Infections = cellulitis or erysipelas, major cutaneous abscess, wound infection
Prokocimer 2013 [212]	Acute bacterial skin and skin structure infections (ABSSSIs)	Randomized double-blind study Intent-to-treat analysis Primary endpoint = FDA criteria (clinical response at 72 hours)	Oral tedizolid 200 mg once daily for 6 days	Oral linezolid 600 mg twice daily for 10 days	Treatment group 1: 332 Treatment group 2: 335	Treatment duration: group 1: 6 days; group 2: 10 days Clinical response on Day 3 (primary endpoint): group 1: 79.5%; group 2: 79.4% (NS) Clinical response on Day 11 (secondary endpoint): group 1: 69.3%; group 2: 71.9% (NS)	
Miller 2015 [210]	Acute bacterial skin and skin structure infections (ABSSSIs) (cellulitis, abscess $\geq$ 5 cm)	Randomized double-blind study	Oral clindamycin	Oral trimetho-prim/sulfamethoxazole	Treatment group 1: 262 Treatment group 2: 262	Treatment duration: group 1: 10 days; group 2: 10 days Clinical recovery rate: group 1: 89.5%; group 2: 88.2% (NS)	

Table 18 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	Number of patients included	Results	Comments
Corey 2014 [219]	Acute bacterial skin and skin structure infections (ABSSSIs)	Randomized double-blind study	IV oritavancin, (single-dose of 1200 mg)	IV vancomycin (15 mg/kg twice daily)	Treatment group 1: 483 Treatment group 2: 485	Treatment duration: group 1: single-dose; group 2: 7 to 10 days Composite efficacy criterion at 48-72 hours: group 1: 82.3%; group 2: 78.9% (NS) Clinical recovery (according to the investigator): group 1: 79.6%; group 2: 80% (NS) Proportion of patients with at least 20% reduction in the lesion size: group 1: 86.9%; group 2: 82.9% (NS)	
Dodds 2009 [220]	Skin and soft tissue infections (SSTIs)	Literature review	Linezolid	Vancomycin		Treatment duration = 4 to 28 days Rates of recovery are not significantly different between both groups	Wide variety of treatment durations in both groups; the optimal treatment duration could not be defined
Boucher 2014 [213]	Complicated skin and soft tissue infections (cSSTIs)	Randomized study Primary endpoint = FDA criteria (clinical response at 72 hours)	Dalbavancin (one infusion on Day 1 and Day 8)	Vancomycin (15 mg/kg twice daily) Vancomycin may be replaced by linezolid after 3 days of treatment	Treatment group 1: 659 Treatment group 2: 653	Treatment duration: group 1: 2 administrations one week apart; group 2: 10 to 14 days Clinical response on Day 3: group 1: 79.7%; group 2: 79.8% (NS)	
Friedland 2012 [221]	Acute bacterial skin and skin structure infections (ABSSSIs based on the FDA definition)	Retrospective study	IV ceftaroline fosamil (600 mg twice daily)	Vancomycin (1 g twice daily) + aztreonam (1 g twice daily)	Treatment group 1: 400 Treatment group 2: 397	Treatment duration: 5 to 14 days Clinical response (defined by apyrexia and by the end of the lesion growth on Day 3): group 1: 74%; group 2: 66.2%	Mean treatment duration by treatment group was not mentioned in the article

Table 18 (*Continued*)

Reference	Infection	Method	Treatment group 1	Treatment group 2	Number of patients included	Results	Comments
Jaurequi 2005 [222]	Complicated skin and skin structure infections (cSSSIs)	Randomized double-blind study	IV dalbavancin (one 1 g-infusion on Day 1 and 500 mg on Day 8)	Linezolid (IV 600 mg twice daily, then switch to the oral route)	Treatment group 1: 571 Treatment group 2: 283	Treatment duration: group 1: one administration on Day 1 and another one on Day 8: group 2: 14 days Clinical recovery rate in clinically assessable patients 14 days after discontinuation of study treatments: group 1: 88.9%; group 2: 91.2% (NS)	Infections = "major" abscess, "substantial" burn, skin and subcutaneous skin infection such as extensive or necrotizing cellulitis, known or suspected skin or subcutaneous skin infection caused by MRSA
Arbeit 2004 [214]	cSSSIs Literature review	Randomized study	IV daptomycin (4 mg/kg/day)	IV antistaphylococcal penicillin (4 to 12 g/day) or vancomycin (1 g twice daily)	Treatment group 1: 534 Treatment group 2: 558	Treatment duration: 7 to 14 days 4 to 7 days were enough for 63% of patients in group 1 vs. 33% in group 2 Rate of recovery among clinically assessable patients: group 1: 83.4%; group 2: 84.2% (NS)	
Quist 2012 [223]	Complicated skin and soft tissue infections (cSSTIs)	Randomized study	IV daptomycin (4 mg/k/day)	IV vancomycin (1 g twice daily) or teicoplanin (400 mg/day)	Treatment group 1: 97 Treatment group 2: 91	Mean treatment duration not specified, but only 4 to 7 days for 75% of patients in group 1 vs. 62% in group 2 Clinical recovery rate in clinically assessable patients: group 1: 91.4%; group 2: 87.2%	
Medeiros 2001 [215]	Antibiotic prophylaxis of animal bites	Cochrane review				Median treatment duration = 5 days	
Stryjewski 2005 [224]	cSSTIs due to Gram-positive bacteria	Randomized double-blind study	IV telavancin (7.5 mg/kg, once daily)	Antistaphylococcal penicillin (four times a day) or vancomycin (twice daily)	Treatment group 1: 84 Treatment group 2: 83	Median treatment duration: group 1: 7 days; group 2: 7 days Clinical recovery rate: group 1: 79%; group 2: 80% (NS)	

Suggested treatment durations:

- 3 days: in the absence of clinical and microbiological documentation:
  - and in the absence of signs of severity,
  - and if the patient is stable,
  - and in the absence of fever for at least 48 hours,
  - and 48-hour hospital surveillance if the agranulocytosis is persisting (immediately start the antibiotic therapy again in case of fever recurrence);
- 7 days: if microbiological documentation[2]:
  - and in the absence of fever for more than 4 days,
  - and microbiological eradication,
  - and resolution of infection clinical signs.

retention in patients still presenting with neutropenia after 7 days. They observed a significantly higher rate of infectious complications in the discontinuation group.

However, the IDSA points to a specific situation: FUO in patients at low-risk of neutropenia > 7 days presenting without any documented infection; switching to an oral treatment may be possible for apyretic patients after 3 days of parenteral antibiotic therapy. Guidelines even suggest discontinuing the antibiotic therapy after 3 days and before neutropenia correction in apyretic patients for at least 24 hours and whose cultures are negative at 48 hours.

Indeed, various studies – mostly pediatric ones – suggest that this approach could be implemented in these situations. Most of these studies are prospective or non-prospective follow-up of patient cohorts (Table 19). The authors of a randomized study [228] of 75 hemodynamically stable children presenting with FUO and CRP < 40 mg/day on Day 1 and 2 did not observe any differences in terms of clinical outcome between antibiotic therapy discontinuation on Day 3 and antibiotic therapy retention until fever and neutropenia resolution. Another randomized pediatric study [229] compared two strategies in 73 patients at low-risk of neutropenia > 7 days and presenting with FUO, apyrexia for 24 hours, in remission, and without any comorbidity. Patients were either discharged with or without oral antibiotic therapy. Readmission rates were low and were similar in both groups.

Discontinuing the antibiotic therapy in case of FUO was not as extensively studied in adults: a non-randomized hematological study compared the outcome of patients presenting with FUO receiving broad-spectrum IV antibiotic therapy and presenting with apyrexia for 48 hours, for whom local guideline was to discontinue the antibiotic therapy [230]. Patient outcome was similar in the discontinuation or retention groups. However, the study sample size was small and the recommendation to discontinue the antibiotic therapy was applied in only 34% of FUO episodes. Similarly, discontinuing the broad-spectrum IV antibiotic therapy after 3 days in patients receiving fluoroquinolone prophylaxis was applied in 53% of patients and did not seem to have any negative clinical repercussions [231]. Conversely, discontinuing the antibiotic therapy in neutropenia patients presenting with persistent fever was associated with failure in 50% of cases [232].

More recently, European guidelines (ECIL group) [226] focusing on all types of neutropenia (patients at low or high-risk of neutropenia > 7 days) recommend this empirical antibiotic therapy discontinuation after 3 days if the following conditions are met: stable hemodynamic status, apyrexia for at least 48 hours, and hospital surveillance within 24–48 hours after discontinuation. This recommendation has, however, been disputed for patients at high-risk of infection who experienced treatment failures [233]. The authors of this prospective study evaluated the early discontinuation of the antibiotic therapy during a febrile neutropenia episode in carefully selected (please see exclusion criteria) patients at high-risk of complications treated for acute myeloid leukemia (AML). Three of the seven included patients experienced early relapse of the infection, including two patients presenting with bacteremia and one with septic shock. These patients had to be withdrawn from the study. The members of the ECIL group published an editorial where they commented on this article, arguing in favor of European guidelines [234].

For microbiologically documented infections, ECIL recommends an antibiotic therapy of at least 7 days with microbiological eradication of the infection, resolution of clinical signs, and at least 4 days without fever [235]. This recommendation is based on data from studies comparing antibiotic monotherapies or combinations instead of various treatment durations.

14.1. Conclusions

For patients presenting with febrile neutropenia, the following antibiotic therapy durations may be prescribed in two very specific situations:

- necrotizing fasciitis without clinical or microbiological documentation (FUO), without signs of severity, stable patients: potential discontinuation (with or without reinitiation of the antibiotic prophylaxis) after 3 days of antibiotic treatment and apyrexia for more than 48 hours, with a 48-hour hospital surveillance, and immediate reinitiation of the antibiotic therapy in case of fever reoccurrence. This strategy seems to be better suited for low-risk patients (solid tumors) than high-risk hematological patients for whom the level of evidence is lower;
- microbiologically documented necrotizing fasciitis: at least until the end of neutropenia or for 7 days in case of fever > 4 days, microbiological eradication, and resolution of clinical signs.

[2] Treatment duration should be tailored to the isolated pathogen and to the potential site of infection.

Table 19
References – febrile neutropenia.
Bibliographie – neutropénie fébrile.

Reference	Patients	Method	Treatment group 1	Treatment group 2	Number of patients or episodes	Results	Statistics	Comments
Hodgson-Viden 2005 [236]	Pediatrics	Retrospective, monocenter study	Antibiotic discontinuation with neutrophil count < 500 cells/mm^3	None	112 patients	Fever recurrence 2/112 No secondarily documented infection	–	Feasible for 56% of patients
Santolaya 1997 [228]	Pediatrics Low-risk (FUO, hemodynamically stable, negative baseline cultures, CRP < 40 mg/l on Day 1 and Day 2)	Prospective, monocenter, randomized, open-label study	IV antibiotic retention until fever and neutropenia resolution	IV antibiotic discontinuation on Day 3	39/36	Favorable outcome: 36/39 (92%) vs. 34/36 (94%) No mortality	$P > 0.5$	Exclusion of cohort patients: 163/238 (68.5%)
Klaassen 2000 [229]	Pediatrics Low-risk (apyrexia > 24 hours, negative blood cultures, no sepsis, disease remission, no comorbidity)	Randomized, controlled, monocenter study	Oral antibiotics administered at home	No antibiotic	37/36	Fever recurrence: 5/37 (14%) vs. 2/36 (6%)	$P = 0.43$	Low-risk
Kaplan 1991 [237]	Pediatrics Low-risk	Retrospective, cohort study	Antibiotic duration: median of 4 days	None	39	Fever recurrence: 4/39 (10%)		Strategy applied to 39/385 episodes (9%)
Cohen J 1995 [240]	Pediatrics Low-risk	Retrospective, cohort study	Antibiotic discontinuation if apyrexia, negative cultures at 48 hours	None	32	6 readmissions to hospital (18%) for fever ($n = 4$) or positive cultures after 48 hours		
Jones 1994 [238]	Pediatrics Group I: solid tumors, leukemia in remission Group II: induction chemotherapy for leukemia patients	Prospective, cohort study	Antibiotic discontinuation in the absence of documentation, negative cultures at 48 hours, and apyrexia > 24 hours	None	83	Fever recurrence: 3/50 (6%) group 1, 15/33 (45%) group 2		This strategy could not be applied for the induction chemotherapy administered to acute leukemia patients

Table 19 (*Continued*)

Reference	Patients	Method	Treatment group 1	Treatment group 2	Number of patients or episodes	Results	Statistics	Comments
Lehrnbecher 2002 [239]	Pediatrics Low-risk	Retrospective study	Antibiotic discontinuation at 72 hours if apyrexia > 24 hours	None	84 episodes	No complication No readmission for fever		Solid tumors Feasible for 84/106 (79%) episodes
Slobbe 2009 [231]	Hematology, adults Neutropenia 10 days Fever of unknown origin Fluoroquinolone prophylaxis	Prospective, observational, monocenter study	Imipenem 3 days Discontinuation in the absence of documentation	None	169 episodes	Mortality: 3/169 (1.7%)	–	Feasible for 53% of patients
Cherif 2004 [230]	Hematology, adults Prospective multicenter study Antibiotic intake for the past 3 days	Comparative, non-randomized study	Antibiotic retention 48 hours after apyrexia	Antibiotic discontinuation 48 hours after apyrexia	29/31	Success: 23 (79%) vs. 26 (83%)	No difference between the groups	Recommendation followed for 34% of FUO
Joshi 1994 [232]	Adults FUO Persistent fever and neutropenia	Prospective, cohort study	Antibiotic discontinuation after 4 days	16	16	Failures 8/16		
Pizzo 1979 [227]	Children and adults Neutropenia >7 days Apyrexia	Randomized, controlled study	Antibiotic retention	Antibiotic discontinuation	33	Infectious complication 0/16 vs. 7/17 (41%) $P = 0.007$	Significant difference	Supporting antibiotic retention until neutropenia correction

FUO: fever of unknown origin; IV: intravenous.

Table 20
Proposals for studies of antibiotic therapy duration.
Propositions d'études sur la durée des antibiothérapies.

Clinical presentation	Duration of reference treatment	Duration of short treatment to be assessed
Acute community-acquired pneumonia	7 days	3 days
Coagulase-negative Staphylococcus catheter-related bacteremia	5 days	Catheter removal without antibiotic administration
Gram-negative bacillus, streptococcal, and enterococcal catheter-related bacteremia	10 days	7 days
Sigmoiditis without surgery	14 days	7 days
Cholecystitis without surgery	14 days	7 days
UTI – Uncomplicated acute cystitis treated with pivmecillinam or nitrofurantoin	5 days	3 days
Catheter-associated urinary tract infections following catheter removal	Single-dose of co-trimoxazole	5 days of co-trimoxazole
Complicated upper reproductive tract infections, with surgery	14 days	7 days
Bone and joint infections	6 to 12 weeks in case of prosthetic joint infection	Prosthetic joint infection = validate 6-week treatment if prosthesis removal, regardless of one-step or two-step procedure
High-risk febrile agranulocytosis without any documentation	Clinical impact of two strategies (antibiotic discontinuation after 48 hours of apyrexia versus antibiotic retention until the end of aplasia)	

The main characteristics of studies considered in this analysis are presented in Table 19.

15. Discussion – conclusion

This work stresses the need for new well-conducted studies evaluating treatment durations for some common infections. Studies are currently ongoing: PHRC PROSTASHORT (randomized placebo-controlled multicenter non-inferiority study comparing the efficacy of a short 7-day antibiotic therapy versus 14 days of treatment in patients presenting with non-nosocomial acute prostatitis caused by fluoroquinolone-susceptible bacteria) or PHRC PCT (randomized placebo-controlled multicenter non-inferiority study comparing the efficacy of 3 days versus 7 days of treatment in patients presenting with mild community-acquired acute pneumonia).

Following the above-mentioned work focusing on existing literature data, the Recommendation Group of the SPILF suggests specific study proposals (Table 20).

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Rapport du groupe de travail spécial pour la préservation des antibiotiques [rapport_antibiotiques.pdf] [Internet]; 2016. http://social-sante.gouv.fr/IMG/pdf/rapport_antibiotiques.pdf [Accessed on April 6, 2016].
[2] Pinzone MR, Cacopardo B, Abbo L, Nunnari G. Review article duration of antimicrobial therapy in community acquired pneumonia: less is more. Sci World J 2014:1–8.
[3] Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 2012;54(8):e72–112.
[4] Hoberman A, Paradise JL, Cohen R. Duration of therapy for acute otitis media. Pediatr Infect Dis J 2000;19(5):471–3.
[5] Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SE, Wincott JL, Sitar DS, Klassen TP, et al. Treatment of acute otitis media with a shortened course of antibiotics: a meta-analysis. JAMA 1998;279(21):1736–42.
[6] Pichichero ME, Cohen R. Shortened course of antibiotic therapy for acute otitis media, sinusitis and tonsillopharyngitis. Pediatr Infect Dis J 1997;16(7):680–95.
[7] Pichichero ME, Marsocci SM, Murphy ML, Hoeger W, Francis AB, Green JL. A prospective observational study of 5-, 7-, and 10-day antibiotic treatment for acute otitis media. Otolaryngol Head Neck Surg 2001;124(4):381–7.
[8] 2011-infections-respir-hautes-recommandations.pdf [Internet]. Available from: http://www.infectiologie.com/UserFiles/File/medias/Recos/2011-infections-respir-hautes-recommandations.pdf [Accessed on February 10, 2016].
[9] Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev 2010;(9):CD001095.
[10] Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AIM. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. Cochrane Database Syst Rev 2012;10:CD006089.
[11] Cohen R, Levy C, Boucherat M, Langue J, Autret E, Gehanno P, et al. Five vs. ten days of antibiotic therapy for acute otitis media in young children. Pediatr Infect Dis J 2000;19(5):458–63.
[12] Cohen R, Levy C, Boucherat M, Langue J, de La Rocque F. A multicenter, randomized, double-blind trial of 5 versus 10 days of antibiotic therapy for acute otitis media in young children. J Pediatr 1998;133(5):634–9.
[13] Casey JR, Pichichero ME. Metaanalysis of short course antibiotic treatment for group a streptococcal tonsillopharyngitis. Pediatr Infect Dis J 2005;24(10):909–17.
[14] Pichichero ME, Casey JR. Bacterial eradication rates with shortened courses of 2nd- and 3rd-generation cephalosporins versus 10 days of penicillin for treatment of group A streptococcal tonsillopharyngitis in adults. Diagn Microbiol Infect Dis 2007;59(2):127–30.
[15] DeMuri GP, Wald ER. Clinical practice. Acute bacterial sinusitis in children. N Engl J Med 2012;367(12):1128–34.

[16] Peyramond D, Portier H, Geslin P, Cohen R, The French Study Group Clamorange. 6-day amoxicillin versus 10-day penicillin V for group A beta-haemolytic streptococcal acute tonsillitis in adults: a French multicentre, open-label, randomized study. Scand J Infect Dis 1996;28(5):497–501.
[17] Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2015;6:CD000219.
[18] Cohen R, Levy C, Doit C, De La Rocque F, Boucherat M, Fitoussi F, et al. Six-day amoxicillin vs. ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. Pediatr Infect Dis J 1996;15(8):678–82.
[19] Société de pathologie infectieuse de langue française, Agence française de sécurité sanitaire des produits de santé. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte; 2010. Available from: http://www.infectiologie.com/site/medias/_documents/consensus/2010-infVRB-spilf-afssaps.pdf [Consulté le 29 juin 2016].
[20] Wunderink RG. A CAP on antibiotic duration. Am J Respir Crit Care Med 2006;174(1):3–5.
[21] Schrag SJ, Peña C, Fernández J, Sánchez J, Gómez V, Pérez E, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA 2001;286(1):49–56.
[22] Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroëdan F, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA 1998;279(5):365–70.
[23] Falagas ME, Avgeri SG, Matthaiou DK, Dimopoulos G, Siempos II. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother 2008;62(3):442–50.
[24] Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003;37(6):752–60.
[25] Mandell LA, File TM. Short-course treatment of community-acquired pneumonia. Clin Infect Dis 2003;37(6):761–3.
[26] Shorr AF, Zadeikis N, Xiang JX, Tennenberg AM, Wes Ely E. A multicenter, randomized, double-blind, retrospective comparison of 5- and 10-day regimens of levofloxacin in a subgroup of patients aged > or = 65 years with community-acquired pneumonia. Clin Ther 2005;27(8):1251–9.
[27] Shorr AF, Khashab MM, Xiang JX, Tennenberg AM, Kahn JB. Levofloxacin 750-mg for 5 days for the treatment of hospitalized Fine Risk Class III/IV community-acquired pneumonia patients. Respir Med 2006;100(12):2129–36.
[28] Drehobl MA, De Salvo MC, Lewis DE, Breen JD. Single-dose azithromycin microspheres vs. clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest 2005;128(4):2230–7.
[29] D'Ignazio J, Camere MA, Lewis DE, Jorgensen D, Breen JD. Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. Antimicrob Agents Chemother 2005;49(10):4035–41.
[30] Blasi F, Tarsia P. Value of short-course antimicrobial therapy in community-acquired pneumonia. Int J Antimicrob Agents 2005;26(Suppl. 3):S148–55.
[31] Moussaoui el R, de Borgie CAJM, van den Broek P, Hustinx WN, Bresser P, van den Berk GEL, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ 2006;332(7554):1355–60.
[32] Leophonte P, Choutet P, Gaillat J, Petitprez P, Portier H, Montestruc F. Efficacy of a ten-day course of ceftriaxone compared to a shortened five-day course in the treatment of community-acquired pneumonia in hospitalized adults with risk factors. Med Mal Infect 2002;32:369–81.
[33] Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006;174(1):84–93.
[34] Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs. standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302(10):1059–66.
[35] Long W, Deng X, Zhang YU, Lu G, Xie J, Tang J. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. Respirol Carlton Vic 2011;16(5):819–24.
[36] Kristoffersen KB, Søgaard OS, Wejse C, Black FT, Greve T, Tarp B, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission – a randomized trial. Clin Microbiol Infect 2009;15(5):481–7.
[37] Smith KJ, Wateska A, Nowalk MP, Raymund M, Lee BY, Zimmerman RK, et al. Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. J Gen Intern Med 2013;28(9):1157–64.
[38] Schuetz P, Muller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Evid Based Child Health Cochrane Rev J 2013;8(4):1297–371.
[39] Li JZ, Winston LG, Moore DH, Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med 2007;120(9):783–90.
[40] Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z, Falagas ME. Short- versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. Drugs 2008;68(13):1841–54.
[41] Avdic E, Cushinotto LA, Hughes AH, Hansen AR, Efird LE, Bartlett JG, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis 2012;54(11):1581–7.
[42] Murray C, Shaw A, Lloyd M, Smith RP, Fardon TC, Schembri S, et al. A multidisciplinary intervention to reduce antibiotic duration in lower respiratory tract infections. J Antimicrob Chemother 2014;69(2):515–8.
[43] WHO. Pocket book of hospital care for children: Second edition [Internet]. WHO. Available from: http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/ [Accessed on January 30, 2016].
[44] Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. Pediatr Infect Dis J 2014;33(2):136–42.
[45] Niederman MS, Chang JR, Stewart J, Asche CV, Lavin B, Nusrat R, et al. Hospitalization rates among patients with community-acquired pneumonia treated with telithromycin vs. clarithromycin: results from two randomized, double-blind, clinical trials. Curr Med Res Opin 2004;20(7):969–80.
[46] Tellier G, Chang JR, Asche CV, Lavin B, Stewart J, Sullivan SD. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. Curr Med Res Opin 2004;20(5):739–47.
[47] Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant G-J. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ 2009;338:b1374.
[48] Cals JWL, Schot MJC, de Jong SAM, Dinant G-J, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med 2010;8(2):124–33.
[49] Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S, Petersen PH, et al. Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. Scand J Prim Health Care 2000;18(1):39–43.
[50] Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;131(1):9–19.
[51] Albrich WC, Dusemund F, Bucher B, Meyer S, Thomann R, Kühn F, et al. Effectiveness and safety of procalcitonin-guided antibiotic therapy in

lower respiratory tract infections in "real life": an international, multicenter poststudy survey (ProREAL). Arch Intern Med 2012;172(9):715–22.
[52] Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs. a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;168(18):2000–7 [discussion 2007–8].
[53] Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet Lond Engl 2004;363(9409):600–7.
[54] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49(1):1–45.
[55] Timsit. Réactualisation de la douzième conférence de consensus de la Société de réanimation de langue française (SRLF) : infections liées aux cathéters veineux centraux en réanimation. Reanimation 2003;12:258–65.
[56] Pigrau C, Rodríguez D, Planes AM, Almirante B, Larrosa N, Ribera E, et al. Management of catheter-related Staphylococcus aureus bacteremia: when may sonographic study be unnecessary? Eur J Clin Microbiol Infect 2003;22(12):713–9.
[57] Raad II, Sabbagh MF. Optimal duration of therapy for catheter-related Staphylococcus aureus bacteremia: a study of 55 cases and review. Clin Infect Dis 1992;14(1):75–82.
[58] Zeylemaker MM, Jaspers CA, van Kraaij MG, Visser MR, Hoepelman IM. Long-term infectious complications and their relation to treatment duration in catheter-related Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect 2001;20(6):380–4.
[59] Ghanem GA, Boktour M, Warneke C, Pham-Williams T, Kassis C, Bahna P, et al. Catheter-related Staphylococcus aureus bacteremia in cancer patients: high rate of complications with therapeutic implications. Medicine (Baltimore) 2007;86(1):54–60.
[60] Malanoski GJ, Samore MH, Pefanis A, Karchmer AW. Staphylococcus aureus catheter-associated bacteremia. Minimal effective therapy and unusual infectious complications associated with arterial sheath catheters. Arch Intern Med 1995;155(11):1161–6.
[61] Ehni WF, Reller LB. Short-course therapy for catheter-associated Staphylococcus aureus bacteremia. Arch Intern Med 1989;149(3):533–6.
[62] Mylotte JM, McDermott C, Spooner JA. Prospective study of 114 consecutive episodes of Staphylococcus aureus bacteremia. Rev Infect Dis 1987;9(5):891–907.
[63] Mylotte JM, McDermott C. Staphylococcus aureus bacteremia caused by infected intravenous catheters. Am J Infect Control 1987;15(1):1–6.
[64] Iannini PB, Crossley K. Therapy of Staphylococcus aureus bacteremia associated with a removable focus of infection. Ann Intern Med 1976;84(5):558–60.
[65] Chong YP, Moon SM, Bang K-M, Park HJ, Park S-Y, Kim M-N, et al. Treatment duration for uncomplicated Staphylococcus aureus bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother 2013;57(3):1150–6.
[66] Corey GR, Stryjewski ME, Everts RJ. Short-course therapy for bloodstream infections in immunocompetent adults. Int J Antimicrob Agents 2009;34(Suppl. 4):S47–51.
[67] Corona A, Wilson APR, Grassi M, Singer M. Prospective audit of bacteraemia management in a university hospital ICU using a general strategy of short-course monotherapy. J Antimicrob Chemother 2004;54(4):809–17.
[68] Corona A, Wilson APR, Grassi M, Singer M. Short-course monotherapy strategy for treating bacteremia in the critically ill. Minerva Anestesiol 2006;72(10):841–57.
[69] De Santis V, Gresoiu M, Corona A, Wilson APR, Singer M. Bacteraemia incidence, causative organisms and resistance patterns, antibiotic strategies and outcomes in a single university hospital ICU: continuing improvement between 2000 and 2013. J Antimicrob Chemother 2015;70(1):273–8.
[70] Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care 2011;15(6):R267.
[71] Park SH, Milstone AM, Diener-West M, Nussenblatt V, Cosgrove SE, Tamma PD. Short versus prolonged courses of antibiotic therapy for children with uncomplicated Gram-negative bacteraemia. J Antimicrob Chemother 2014;69(3):779–85.
[72] Daneman N, Rishu AH, Xiong W, Bagshaw SM, Cook DJ, Dodek P, et al. Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE): study protocol for a pilot randomized controlled trial. Trials 2015;16:173.
[73] Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30(19):2369–413.
[74] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015.
[75] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(22):e57–185.
[76] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(22):2438–88.
[77] Olaison L, Schadewitz K, Swedish Society of Infectious Diseases Quality Assurance Study Group for Endocarditis. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis 2002;34(2):159–66.
[78] Dahl A, Rasmussen RV, Bundgaard H, Hassager C, Bruun LE, Lauridsen TK, et al. Enterococcus faecalis infective endocarditis: a pilot study of the relationship between duration of gentamicin treatment and outcome. Circulation 2013;127(17):1810–7.
[79] Francioli P, Ruch W, Stamboulian D. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. Clin Infect Dis 1995;21(6):1406–10.
[80] Ribera E, Gómez-Jimenez J, Cortes E, del Valle O, Planes A, Gonzalez-Alujas T, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided Staphylococcus aureus endocarditis. A randomized, controlled trial. Ann Intern Med 1996;125(12):969–74.
[81] DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by Staphylococcus aureus in injection drug users. Ann Intern Med 1994;121(11):873–6.
[82] Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. J Antimicrob Chemother 2006;57(4):639–47.
[83] Leibovici L. Aminoglycoside-containing antibiotic combinations for the treatment of bacterial endocarditis: an evidence-based approach. Int J Antimicrob Agents 2010;36(Suppl. 2):S46–9.
[84] Sandoe JAT, Barlow G, Chambers JB, Gammage M, Guleri A, Howard P, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). J Antimicrob Chemother 2015;70(2):325–59.

[85] Hoen B, Duval X. Infective endocarditis. N Engl J Med 2013;369(8):785.
[86] Sexton DJ, Tenenbaum MJ, Wilson WR, Steckelberg JM, Tice AD, Gilbert D, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Clin Infect Dis 1998;27(6):1470–4.
[87] Korzeniowski O, Sande MA. Combination antimicrobial therapy for Staphylococcus aureus endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. Ann Intern Med 1982;97(4):496–503.
[88] Abrams B, Sklaver A, Hoffman T, Greenman R. Single or combination therapy of staphylococcal endocarditis in intravenous drug abusers. Ann Intern Med 1979;90(5):789–91.
[89] Coppens L, Hanson B, Klastersky J. Therapy of staphylococcal infections with cefamandole or vancomycin alone or with a combination of cefamandole and tobramycin. Antimicrob Agents Chemother 1983;23(1):36–41.
[90] Rajashekaraiah KR, Rice T, Rao VS, Marsh D, Ramakrishna B, Kallick CA. Clinical significance of tolerant strains of Staphylococcus aureus in patients with endocarditis. Ann Intern Med 1980;93(6):796–801.
[91] Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39(9):1267–84.
[92] Société de pathologie infectieuse de langue française. [17th Consensus conference. Consensus conference on bacterial meningitis. Short text]. Med Mal Infect 2009;39(3):175–86.
[93] Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty JF, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. Lancet 2005;366(9482):308–13.
[94] Briggs S, Ellis-Pegler R, Roberts S, Thomas M, Woodhouse A. Short course intravenous benzylpenicillin treatment of adults with meningococcal disease. Intern Med J 2004;34(7):383–7.
[95] Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. Arch Dis Child 2009;94(8):607–14.
[96] Molyneux E, Nizami SQ, Saha S, Huu KT, Azam M, Bhutta ZA, et al. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. Lancet Lond Engl 2011;377(9780):1837–45.
[97] Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50(2):133–64.
[98] Montravers P, Dupont H, Leone M, Constantin J-M, Mertes P-M, Société française d'anesthésie et de réanimation (Sfar), et al. Guidelines for management of intra-abdominal infections. Anaesth Crit Care Pain Med 2015;34(2):117–30.
[99] Riccio LM, Popovsky KA, Hranjec T, Politano AD, Rosenberger LH, Tura KC, et al. Association of excessive duration of antibiotic therapy for intra-abdominal infection with subsequent extra-abdominal infection and death: a study of 2,552 consecutive infections. Surg Infect 2014;15(4):417–24.
[100] Basoli A, Chirletti P, Cirino E, D'Ovidio NG, Doglietto GB, Giglio D, et al. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 vs. >or=5 days in community-acquired intraabdominal infection. J Gastrointest Surg 2008;12(3):592–600.
[101] Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 2015;372(21):1996–2005.
[102] Montravers P, Tubach F, Esposito-Farese M, Lasocki S, Lescot T, Veber B. Duration of antibiotic therapy in post-operative peritonitis: the DURAPOP study. In: 26th ECCMID. 2016 [abstract O334].
[103] de Korte N, Unlü C, Boermeester MA, Cuesta MA, Vrouenreats BC, Stockmann HB, et al. Use of antibiotics in uncomplicated diverticulitis. Br J Surg 2011;98(6):761–7.
[104] Morris AM, Regenbogen SE, Hardiman KM, Hendren S. Sigmoid diverticulitis: a systematic review. JAMA 2014;311(3):287–97.
[105] Shabanzadeh DM, Wille-Jørgensen P. Antibiotics for uncomplicated diverticulitis. Cochrane Database Syst Rev 2012;11:CD009092.
[106] Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg 2012;99(4):532–9.
[107] Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management – a prospective study of 542 patients. Eur Radiol 2002;12(5):1145–9.
[108] Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology 1991;100(6):1737–42.
[109] Rimola A, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32(1):142–53.
[110] Fernández J, Gustot T. Management of bacterial infections in cirrhosis. J Hepatol 2012;56(Suppl. 1):S1–12.
[111] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60(6):1310–24.
[112] Prise en charge des complications des cirrhoses – Argumentaire [Internet]. Available from: http://www.has-sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_670742 [Accessed on January 16, 2016].
[113] Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014;312(2):145–54.
[114] Lau WY, Yuen WK, Chu KW, Chong KK, Li AK. Systemic antibiotic regimens for acute cholecystitis treated by early cholecystectomy. Aust N Z J Surg 1990;60(7):539–43.
[115] Yoshida M, Takada T, Kawarada Y, Tanaka A, Nimura Y, Gomi H, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg 2007;14(1):83–90.
[116] Mazeh H, Mizrahi I, Dior U, Simanovsky N, Shapiro M, Freund HR, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg 2012;36(8):1750–9.
[117] Kogure H, Tsujino T, Yamamoto K, Mizuno S, Yashima Y, Yagioka H, et al. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. J Gastroenterol 2011;46(12):1411–7.
[118] van Lent AUG, Bartelsman JFWM, Tytgat GNJ, Speelman P, Prins JM. Duration of antibiotic therapy for cholangitis after successful endoscopic drainage of the biliary tract. Gastrointest Endosc 2002;55(4):518–22.
[119] hcspr20100129_gastro.pdf [Internet]. Available from: http://www.hcsp.fr/explore.cgi/hcspr20100129_gastro.pdf [Accessed on January 16, 2016].
[120] DuPont HL, Ericsson CD, Mathewson JJ, DuPont MW. Five versus three days of ofloxacin therapy for traveler's diarrhea: a placebo-controlled study. Antimicrob Agents Chemother 1992;36(1):87–91.
[121] Tribble DR, Sanders JW, Pang LW, Mason C, Pitarangsi C, Baqar S, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. Clin Infect Dis 2007;44(3):338–46.
[122] Bennish ML, Salam MA, Khan WA, Khan AM. Treatment of shigellosis: III. Comparison of one- or two-dose ciprofloxacin with standard 5-day therapy. A randomized, blinded trial. Ann Intern Med 1992;117(9):727–34.
[123] Butler T. Treatment of typhoid fever in the 21st century: promises and shortcomings. Clin Microbiol Infect 2011;17(7):959–63.
[124] Chinh NT, Parry CM, Ly NT, Ha HD, Thong MX, Diep TS, et al. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. Antimicrob Agents Chemother 2000;44(7):1855–9.

[125] Frenck RW, Mansour A, Nakhla I, Sultan Y, Putnam S, Wierzba T, et al. Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. Clin Infect Dis 2004;38(7):951–7.
[126] Butler T, Sridhar CB, Daga MK, Pathak K, Pandit RB, Khakhria R, et al. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999;44(2):243–50.
[127] Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases, European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014;20(Suppl. 2):1–26.
[128] Schug-Pass C, Geers P, Hügel O, Lippert H, Köckerling F. Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis. Int J Colorectal Dis 2010;25(6):751–9.
[129] Alonso S, Pera M, Parés D, Pascual M, Gil MJ, Courtier R, et al. Outpatient treatment of patients with uncomplicated acute diverticulitis. Colorectal Dis 2010;12(10 Online):e278–82.
[130] Hjern F, Josephson T, Altman D, Holmström B, Mellgren A, Pollack J, et al. Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? Scand J Gastroenterol 2007;42(1):41–7.
[131] Gotuzzo E, Oberhelman RA, Maguiña C, Berry SJ, Yi A, Guzman M, et al. Comparison of single-dose treatment with norfloxacin and standard 5-day treatment with trimethoprim-sulfamethoxazole for acute shigellosis in adults. Antimicrob Agents Chemother 1989;33(7):1101–4.
[132] Caron F. [Diagnosis and treatment of community-acquired urinary tract infections in adults: what has changed. Comments on the 2008 guidelines of the French Health Products Safety Agency (AFSSAPS)]. Presse Med 2010;39(1):42–8.
[133] Recommandations bonne pratique pour la prise en charge et la prevention des infections urinaires associées aux soins de l'adulte 2015 [Internet]. Available from: http://sf2h.net/actus/recommandations_bonne-pratique-pour-la-prise-en-charge-et-la-prevention-des-infections-urinaires-associees-aux-soins-de-l-adulte-2015.pdf [Accessed on January 16, 2016].
[134] Nicolle LE, Madsen KS, Debeeck GO, Blochlinger E, Borrild N, Bru JP, et al. Three days of pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection in women. Scand J Infect Dis 2002;34(7):487–92.
[135] Kavatha D, Giamarellou H, Alexiou Z, Vlachogiannis N, Pentea S, Gozadinos T, et al. Cefpodoxime-proxetil versus trimethoprim-sulfamethoxazole for short-term therapy of uncomplicated acute cystitis in women. Antimicrob Agents Chemother 2003;47(3):897–900.
[136] Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med 2007;167(20):2207–12.
[137] Harding GK, Nicolle LE, Ronald AR, Preiksaitis JK, Forward KR, Low DE, et al. How long should catheter-acquired urinary tract infection in women be treated? A randomized controlled study. Ann Intern Med 1991;114(9):713–9.
[138] Mohler JL, Cowen DL, Flanigan RC. Suppression and treatment of urinary tract infection in patients with an intermittently catheterized neurogenic bladder. J Urol 1987;138(2):336–40.
[139] Dow G, Rao P, Harding G, Brunka J, Kennedy J, Alfa M, et al. A prospective, randomized trial of 3 or 14 days of ciprofloxacin treatment for acute urinary tract infection in patients with spinal cord injury. Clin Infect Dis 2004;39(5):658–64.
[140] Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–20.
[141] Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology 2008;71(1):17–22.
[142] Talan DA, Klimberg IW, Nicolle LE, Song J, Kowalsky SF, Church DA. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol 2004;171(2 Pt 1):734–9.
[143] Ulleryd P, Sandberg T. Ciprofloxacin for 2 or 4 weeks in the treatment of febrile urinary tract infection in men: a randomized trial with a 1 year follow-up. Scand J Infect Dis 2003;35(1):34–9.
[144] Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection – 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2013;68(10):2183–91.
[145] Mise au point : traitement antibiotique probabliste des urétrites et cervicites non compliquées, afssaps; 2008. www.ansm.sante.fr [consulté le 29 juin 2016].
[146] Urétrites et cervicites non compliquées : stratégie diagnostique et thérapeutique de prise en charge; 2016. www.has-sante.fr [consulté le 29 juin 2016].
[147] Workowski KA. Centers for disease control and prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis 2015;61(Suppl. 8):S759–62.
[148] SUN/1ann/8p – apercu [Internet]. Available from: http://www.cngof.fr/pratiques-cliniques/recommandations-pour-la-pratique-clinique/apercu?path=RPC%2BCOLLEGE%252FRPC_infections_2012.pdf&i=459 [Accessed on March 6, 2016].
[149] Ross J, Judlin P, Jensen J. International Union against sexually transmitted infections. 2012 European guideline for the management of pelvic inflammatory disease. Int J STD AIDS 2014;25(1):1–7.
[150] Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A, Ambulatory PID Research Group. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. South Med J 1993;86(6):604–10.
[151] Witte EH, Peters AA, Smit IB, van der Linden MC, Mouton RP, van der Meer JW, et al. A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. Eur J Obstet Gynecol Reprod Biol 1993;50(2):153–8.
[152] Arredondo JL, Diaz V, Gaitan H, Maradiegue E, Oyarzún E, Paz R, et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. Clin Infect Dis 1997;24(2):170–8.
[153] Hemsell DL, Martens MG, Faro S, Gall S, McGregor JA. A multicenter study comparing intravenous meropenem with clindamycin plus gentamicin for the treatment of acute gynecologic and obstetric pelvic infections in hospitalized women. Clin Infect Dis 1997;24(Suppl. 2):S222–30.
[154] Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment of acute pelvic inflammatory disease. J Int Med Res 2003;31(1):45–54.
[155] Ross JDC, Cronjé HS, Paszkowski T, Rakoczi I, Vildaite D, Kureishi A, et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. Sex Transm Infect 2006;82(6):446–51.
[156] Savaris RF, Teixeira LM, Torres TG, Edelweiss MIA, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110(1):53–60.
[157] Heystek M, Ross JDC, PID Study Group. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. Int J STD AIDS 2009;20(10):690–5.
[158] Judlin P, Liao Q, Liu Z, Reimnitz P, Hampel B, Arvis P. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. BJOG 2010;117(12):1475–84.

[159] Aşicioğlu O, Gungorduk K, Ozdemir A, Ertas IE, Yildirim G, Sanci M, et al. Single daily dose of moxifloxacin versus ofloxacin plus metronidazole as a new treatment approach to uncomplicated pelvic inflammatory disease: a multicentre prospective randomized trial. Eur J Obstet Gynecol Reprod Biol 2013;171(1):116–21.
[160] Manhart LE, Jensen JS, Bradshaw CS, Golden MR, Martin DH. Efficacy of antimicrobial therapy for mycoplasma genitalium Infections. Clin Infect Dis 2015;61(Suppl. 8):S802–17.
[161] Trautmann GM, Kip KE, Richter HE, Soper DE, Peipert JF, Nelson DB, et al. Do short-term markers of treatment efficacy predict long-term sequelae of pelvic inflammatory disease? Am J Obstet Gynecol 2008;198(1), 30.e1–30.e7.
[162] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004;351(16):1645–54.
[163] Société de pathologie infectieuse de langue française (SPILF), Collège des universitaires de maladies infectieuses et tropicales (CMIT), Groupe de Pathologie infectieuse pédiatrique (GPIP), Société française d'anesthésie et de réanimation (SFAR), Société française de chirurgie orthopédique et traumatologique (SOFCOT), Société française d'hygiène hospitalière (SFHH), et al. Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis). Med Mal Infect 2010;40(4):185–211.
[164] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56(1):1–10.
[165] Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J 2013;95B(11): 1450–2.
[166] Minassian AM, Osmon DR, Berendt AR. Clinical guidelines in the management of prosthetic joint infection. J Antimicrob Chemother 2014;69(Suppl. 1):i29–35.
[167] Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE, Foreign-Body Infection (FBI) Study Group. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. JAMA 1998;279(19):1537–41.
[168] Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, et al. A large multicenter study of methicillin-susceptible and methicillin-resistant Staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis 2013;56(2):182–94.
[169] Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect 2010;61(2):125–32.
[170] Berdal J-E, Skråmm I, Mowinckel P, Gulbrandsen P, Bjørnholt JV. Use of rifampicin and ciprofloxacin combination therapy after surgical debridement in the treatment of early manifestation prosthetic joint infections. Clin Microbiol Infect 2005;11(10):843–5.
[171] Westberg M, Grøgaard B, Snorrason F. Early prosthetic joint infections treated with debridement and implant retention: 38 primary hip arthroplasties prospectively recorded and followed for median 4 years. Acta Orthop 2012;83(3):227–32.
[172] Zeller V, Lhotellier L, Marmor S, Leclerc P, Krain A, Graff W, et al. One-stage exchange arthroplasty for chronic periprosthetic hip infection: results of a large prospective cohort study. J Bone Joint Surg Am 2014;96(1):e1.
[173] Farhad R, Roger P-M, Albert C, Pélligri C, Touati C, Dellamonica P, et al. Six weeks antibiotic therapy for all bone infections: results of a cohort study. Eur J Clin Microbiol Infect Dis 2010;29(2):217–22.
[174] Puhto A-P, Puhto T, Syrjala H. Short-course antibiotics for prosthetic joint infections treated with prosthesis retention. Clin Microbiol Infect 2012;18(11):1143–8.
[175] Stockley I, Mockford BJ, Hoad-Reddick A, Norman P. The use of two-stage exchange arthroplasty with depot antibiotics in the absence of long-term antibiotic therapy in infected total hip replacement. J Bone Joint Surg Br 2008;90(2):145–8.
[176] Chaussade. Treatment associated with 6 weeks antibiotic is effective. In: ICAAC. 2013 [Abstract H 1006].
[177] Bassetti M, Vitale F, Melica G, Righi E, Di Biagio A, Molfetta L, et al. Linezolid in the treatment of Gram-positive prosthetic joint infections. J Antimicrob Chemother 2005;55(3):387–90.
[178] Hsieh P-H, Huang K-C, Lee P-C, Lee MS. Two-stage revision of infected hip arthroplasty using an antibiotic-loaded spacer: retrospective comparison between short-term and prolonged antibiotic therapy. J Antimicrob Chemother 2009;64(2):392–7.
[179] McKenna PB, O'Shea K, Masterson EL. Two-stage revision of infected hip arthroplasty using a shortened post-operative course of antibiotics. Arch Orthop Trauma Surg 2009;129(4):489–94.
[180] Whittaker JP, Warren RE, Jones RS, Gregson PA. Is prolonged systemic antibiotic treatment essential in two-stage revision hip replacement for chronic Gram-positive infection? J Bone Joint Surg Br 2009;91(1):44–51.
[181] Mittal Y, Fehring TK, Hanssen A, Marculescu C, Odum SM, Osmon D. Two-stage reimplantation for periprosthetic knee infection involving resistant organisms. J Bone Joint Surg Am 2007;89(6):1227–31.
[182] Brandt CM, Sistrunk WW, Duffy MC, Hanssen AD, Steckelberg JM, Ilstrup DM, et al. Staphylococcus aureus prosthetic joint infection treated with debridement and prosthesis retention. Clin Infect Dis 1997;24(5):914–9.
[183] Laffer RR, Graber P, Ochsner PE, Zimmerli W. Outcome of prosthetic knee-associated infection: evaluation of 40 consecutive episodes at a single centre. Clin Microbiol Infect 2006;12(5):433–9.
[184] Vilchez F, Martínez-Pastor JC, García-Ramiro S, Bori G, Maculé F, Sierra J, et al. Outcome and predictors of treatment failure in early post-surgical prosthetic joint infections due to Staphylococcus aureus treated with debridement. Clin Microbiol Infect 2011;17(3):439–44.
[185] http://www.infectiologie.com/UserFiles/File/medias/_documents/consensus/inf-osseuse-long.pdf [Accessed on January 28, 2016].
[186] Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJG, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54(12):e132–73.
[187] Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev 2013;9:CD004439.
[188] Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care 2015;38(4):735.
[189] Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis 2005;9(3):127–38.
[190] Choutet P, Desplaces N, Evrard. Traitement des infections ostéo-articulaires bactériennes en dehors des infections à mycobactéries. Med Mal Infect 1991;21:546–50.
[191] Coakley G, Mathews C, Field M, Jones A, Kingsley G, Walker D, et al. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. Rheumatology 2006;45(8):1039–41.
[192] Zeller V, Desplaces N. Antibiothérapie des infections ostéoarticulaires à pyogènes chez l'adulte : principes et modalités. Rev Rhum 2006;73:183–90.
[193] Nolla JM, Lora-Tamayo J, Gómez Vaquero C, Narváez J, Murillo O, Pedrero S, et al. Pyogenic arthritis of native joints in non-intravenous drug users: a detailed analysis of 268 cases attended in a tertiary hospital over a 22-year period. Semin Arthritis Rheum 2015;45(1):94–102.
[194] Uçkay I, Tovmirzaeva L, Garbino J, Rohner P, Tahintzi P, Suvà D, et al. Short parenteral antibiotic treatment for adult septic arthritis after successful drainage. Int J Infect Dis 2013;17(3):e199–205.
[195] http://www.infectiologie.com/UserFiles/File/medias/_documents/consensus/2007-Spondylodiscites-Reco.pdf [Accessed on January 28, 2016].
[196] Roblot F, Besnier JM, Juhel L, Vidal C, Ragot S, Bastides F, et al. Optimal duration of antibiotic therapy in vertebral osteomyelitis. Semin Arthritis Rheum 2007;36(5):269–77.
[197] Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet 2015;385(9971):875–82.

[198] Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis 2015;61(6):e26–46.
[199] Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med 2004;164(15):1669–74.
[200] Acute bacterial skin and skin structure infections: developing drugs for treatment [ucm071185.pdf] [Internet]; 2016. http://www.fda.gov/downloads/Drugs/./Guidances/ucm071185.pdf [Accessed on February 10, 2016].
[201] Veyssier-Belot C, Lecomte F. [Consensus conference on erysipelas and necrotizing fasciitis, Tours, January 26, 2000]. Rev Med Interne 2000;21(8):655–8.
[202] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59(2):e10–52.
[203] Bergkvist PI, Sjöbeck K. Antibiotic and prednisolone therapy of erysipelas: a randomized, double blind, placebo-controlled study. Scand J Infect Dis 1997;29(4):377–82.
[204] Bernard P, Plantin P, Roger H, Sassolas B, Villaret E, Legrain V, et al. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. Br J Dermatol 1992;127(2):155–9.
[205] Dall L, Peterson S, Simmons T, Dall A. Rapid resolution of cellulitis in patients managed with combination antibiotic and anti-inflammatory therapy. Cutis 2005;75(3):177–80.
[206] Pallin DJ, Binder WD, Allen MB, Lederman M, Parmar S, Filbin MR, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Clin Infect Dis 2013;56(12):1754–62.
[207] Aboltins CA, Hutchinson AF, Sinnappu RN, Cresp D, Risteski C, Kathirgamanathan R, et al. Oral versus parenteral antimicrobials for the treatment of cellulitis: a randomized non-inferiority trial. J Antimicrob Chemother 2015;70(2):581–6.
[208] Breedt J, Teras J, Gardovskis J, Maritz FJ, Vaasna T, Ross DP, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. Antimicrob Agents Chemother 2005;49(11):4658–66.
[209] Chuang Y-C, Chang C-M, Aradhya S, Nagari B, Pai V, Dartois N, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect 2011;44(2):116–24.
[210] Miller LG, Daum RS, Creech CB, Young D, Downing MD, Eells SJ, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med 2015;372(12):1093–103.
[211] Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2014;14(8):696–705.
[212] Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs. linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA 2013;309(6):559–69.
[213] Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med 2014;370(23):2169–79.
[214] Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38(12):1673–81.
[215] Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites. Cochrane Database Syst Rev 2001;(2):CD001738.
[216] Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005;49(6):2260–6.
[217] Itani KMF, Dryden MS, Bhattacharyya H, Kunkel MJ, Baruch AM, Weigelt JA. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus. Am J Surg 2010;199(6):804–16.
[218] Stevens DL, Smith LG, Bruss JB, McConnell-Martin MA, Duvall SE, Todd WM, et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2000;44(12):3408–13.
[219] Corey GR, Kabler H, Mehra P, Gupta S, Overcash JS, Porwal A, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med 2014;370(23):2180–90.
[220] Dodds TJ, Hawke CI. Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). ANZ J Surg 2009;79(9):629–35.
[221] Friedland HD, O'Neal T, Biek D, Eckburg PB, Rank DR, Llorens L, et al. CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2012;56(5):2231–6.
[222] Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis 2005;41(10):1407–15.
[223] Quist SR, Fierlbeck G, Seaton RA, Loeffler J, Chaves RL. Comparative randomised clinical trial against glycopeptides supports the use of daptomycin as first-line treatment of complicated skin and soft-tissue infections. Int J Antimicrob Agents 2012;39(1):90–1.
[224] Stryjewski ME, Graham DR, Wilson SE, O'Riordan W, Young D, Lentnek A, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 2008;46(11):1683–93.
[225] Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 2011;52(4):e56–93.
[226] Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98(12):1826–35.
[227] Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Levine AS, Deisseroth AB, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med 1979;67(2):194–200.
[228] Santolaya ME, Villarroel M, Avendaño LF, Cofré J. Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis 1997;25(1):92–7.
[229] Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. J Pediatr Hematol Oncol 2000;22(5):405–11.
[230] Cherif H, Björkholm M, Engervall P, Johansson P, Ljungman P, Hast R, et al. A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. Scand J Infect Dis 2004;36(8):593–600.
[231] Slobbe L, van der Waal L, Jongman LR, Lugtenburg PJ, Rijnders BJA. Three-day treatment with imipenem for unexplained fever during prolonged neutropaenia in haematology patients receiving fluoroquinolone and fluconazole prophylaxis: a prospective observational safety study. Eur J Cancer 2009;45(16):2810–7.
[232] Joshi JH, Schimpff SC, Tenney JH, Newman KA, de Jongh CA. Can antibacterial therapy be discontinued in persistently febrile granulocytopenic cancer patients? Am J Med 1984;76(3):450–7.

[233] Micol J-B, Chahine C, Woerther P-L, Ghez D, Netzer F, Dufour C, et al. Discontinuation of empirical antibiotic therapy in neutropenic acute myeloid leukaemia patients with fever of unknown origin: is it ethical? Clin Microbiol Infect 2014;20(7):O453–5.

[234] Orasch C, Averbuch D, Mikulska M, Cordonnier C, Livermore DM, Gyssens IC, et al. Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical. Clin Microbiol Infect 2015;21(3):e25–7.

[235] Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica 2013;98(12):1836–47.

[236] Hodgson-Viden H, Grundy PE, Robinson JL. Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. BMC Pediatr 2005;5(1):10.

[237] Kaplan AH, Weber DJ, Davis L, Israel F, Wells RJ. Short courses of antibiotics in selected febrile neutropenic patients. Am J Med Sci 1991;302(6):353–4.

[238] Jones GR, Konsler GK, Dunaway RP, Gold SH, Cooper HA, Wells RJ. Risk factors for recurrent fever after the discontinuation of empiric antibiotic therapy for fever and neutropenia in pediatric patients with a malignancy or hematologic condition. J Pediatr 1994;124(5 Pt 1):703–8.

[239] Lehrnbecher T, Stanescu A, Kühl J. Short courses of intravenous empirical antibiotic treatment in selected febrile neutropenic children with cancer. Infection 2002;30(1):17–21.

[240] Cohen KJ, Leamer K, Odom L, Greffe B, Stork L. Cessation of antibiotics regardless of ANC is safe in children with febrile neutropenia. A preliminary prospective trial. J Pediatr Hematol Oncol 1995;17(4):325–30.

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Original article

Knowledge of antibiotics and antibiotic resistance in patients followed by family physicians

Facteurs associés à la connaissance des antibiotiques et à leur résistance chez les patients consultant en médecine générale

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Abstract

Objective. – We aimed to evaluate factors associated with knowledge of antibiotics and drug resistance.

Methods. – A questionnaire was handed out by 14 family physicians to their patients between December 20, 2014 and April 20, 2015 in Rethel (North-East of France). We conducted a cross-sectional study using a logistical regression model to assess factors associated with antibiotic knowledge. Three criteria were used to assess that knowledge.

Results. – Overall, 293 questionnaires were analysed; 48% of patients had received antibiotics in the previous 12 months. Only 44% and 26% gave a correct answer for the statements "Antibiotics are effective against bacteria and ineffective against viruses" and "Antibiotic resistance decreases if the antibiotic use decreases", respectively. Characteristics such as female sex, age > 30 years, high level of education, high professional categories, and having received antibiotic information by the media were associated with high level of knowledge about antibiotics and/or antibiotic resistance. In contrast, having received antibiotic information from family physicians was not associated with good knowledge.

Conclusion. – Although media awareness campaigns had an independent impact on a higher public knowledge of antibiotics, the overall public knowledge remains low. It would be necessary to strengthen antibiotic campaigns with clearer information on the relation between the excessive use of antibiotics and the increased risk of antibiotic resistance. Family physicians should be more involved to improve antibiotic knowledge among target groups such as men, young patients, and people from a poor social and cultural background.

Keywords: Antibiotics; Antibiotic resistance; Family physician

Résumé

Objectifs. – Évaluer les facteurs associés aux connaissances des patients sur les antibiotiques et la résistance bactérienne.

Méthode. – Du 20/12/2014 au 20/04/2015, un questionnaire a été distribué dans 14 cabinets médicaux de la ville de Rethel (Ardennes). Dans cette étude transversale analytique, les facteurs associés à la connaissance des antibiotiques ont été identifiés par une régression logistique. Trois critères ont été utilisés pour évaluer le niveau de connaissance.

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Résultats. – Au total, 293 patients ont été inclus dans l'étude. Une consommation d'antibiotiques dans l'année était notée dans 48 % des cas. Seulement 44 % et 26 % des patients savaient que les antibiotiques étaient efficaces contre les bactéries et inefficaces contre les virus et que la résistance aux antibiotiques diminuait si la prescription d'antibiotiques diminuait. Le sexe féminin, l'âge > 30 ans, le niveau d'étude ≥ baccalauréat, la profession cadre et/ou profession médicale et les informations reçues dans les médias étaient les caractéristiques des patients indépendamment associées à une bonne connaissance des antibiotiques et/ou des résistances bactériennes alors que les informations reçues du médecin généraliste ne l'étaient pas.

Conclusion. – Malgré l'efficacité des campagnes d'information sur l'éducation des patients, la connaissance des antibiotiques reste médiocre. Les campagnes médiatiques devraient donc être intensifiées en étant plus claires sur le lien entre la résistance bactérienne et la consommation d'antibiotiques. Professionnels de santé et notamment médecins généralistes pourraient améliorer la connaissance des antibiotiques au sein des catégories peu informées (hommes, jeunes et personnes avec un faible niveau socioculturel).

Mots clés : Antibiotiques ; Résistance bactérienne ; Médecine générale

1. Introduction

The annual consumption of antibiotics in France is one of the highest in Europe. It was estimated at 29.6 daily-defined doses (DDD) in 2012, while the mean European figure was 21.3 DDD. France was thus the fourth European country with the highest antibiotic consumption, after Greece, Romania, and Belgium while it was in first position from 1997 to 2002 [1,2]. Following the first awareness campaign aimed at the general public and family physicians (FPs) in 2002, a 16% decrease in antibiotic consumption was observed between 1999 and 2009 [3]. However, the impact of such campaigns has lessened as a 5.9% yearly increase in the consumption of antibiotics may be observed since 2010 [1].

This high consumption is due to the excessive prescription of antibiotics for viral infections: more than a quarter of antibiotics prescribed in community settings in 2009 [4]. Patients asking FPs for antibiotics is one of the reasons of this high figure [5–7]. The excessive consumption of antibiotics contributes to the emergence of highly resistant bacteria; which dissemination has increased worldwide [8,9]. To fight against the emergence of resistant bacteria, persuasive and/or restrictive measures aimed at FPs have been tested out in several countries: regular antibiotic therapy training, access to educational material, withdrawal of some antibiotics from reimbursement, and/or antimicrobial susceptibility testing limited to five antibiotics [10,11]. Another action taken in this fight consists in improving patient knowledge to raise their awareness of bacterial resistance to antibiotics [12–15].

We aimed to assess factors associated with antibiotic and antibiotic resistance knowledge among patients consulting their FP. We chose to conduct our study in the city and outskirt of Rethel in the Ardennes department (North-East of France). It is a rural area of 36,623 inhabitants in 2011, of whom 8053 lived in the city itself [16].

2. Patients and methods

We contacted all medical practices in Rethel and in its outskirt between December 20, 2014 and April 20, 2015, and invited them to take part in our descriptive and cross-sectional study. We handed over 25 questionnaires ($n = 350$) in each recruited medical practice. To avoid any selection bias, we decided to ask every patient aged ≥ 18 years and every parent of children consulting at the recruited practices if they were willing to complete the questionnaire. The 25 first patients agreeing to complete the questionnaire were selected.

2.1. Questionnaire design

The questionnaire consisted of multiple choice questions with two or three answers to choose from (most often: yes/no/unknown), and of three sections:

- the first section focused on epidemiological data; sex, age, occupation, parent of a child aged ≤ 16 years, smoking status, presenting with a long-term illness, benefiting from the universal medical coverage (French acronym CMU), presenting with diabetes/asthma/respiratory failure; number of years consulting that specific FP, number of consultations/year, potential sources of information on antibiotics (media, social networks, relatives, FP); opinion related to antibiotics, self-medication, and antibiotic consumption in the previous 12 months;
- the second section focused on the patient's knowledge of antibiotics – target and activity (10 questions). We used the following ranking scale: one point per correct answer, no point allocated for incorrect or "unknown" answers. Scores ranged from 0 to 10. We used two specific criteria to define the meaning of "good knowledge of antibiotics":
  - being aware of antibiotic target: effective against bacteria and ineffective against viruses,
  - having a score higher than the mean score obtained by the studied population, i.e., a score ≥ 6/10.
- the third section focused on bacterial resistance to antibiotics (6 questions) and used the same ranking system (scores from 0 to 6). Good knowledge of bacterial resistance to antibiotics was defined by a score higher than the mean score of the studied population: ≥ 3/6.

The questionnaire was first tested on 10 patients to assess its intelligibility as well as the time required to fill it in (approximately 5 minutes).

2.2. Legal consideration

The IT file created for the purpose of the study was subjected to a declaration (no. 1860108v0) to the French Data Protection Authority (French acronym CNIL).

2.3. Analysis

We had initially divided the level of education into seven categories in the questionnaire, according to the last diploma received. We then chose to set as the reference variable high school graduation because results were similar for patients with a level of education higher than high school graduation. We also used the classification of occupational groups issued by the French National Institute for Statistics and Economic Studies (French acronym INSEE) in 2003 [17].

Questionnaire results were analyzed using the Epi-info software 3.5. Quantitative variables were expressed as means (±standard deviation) and qualitative variables as frequencies and percentages. We used Chi^2 test (or Fischer's exact test for smaller frequencies) to compare qualitative variables, and Mann-Whitney test for quantitative variables. The multivariate analysis was performed using a logistical regression model. All variables with a P-value < 0.05 in the univariate analysis were included in the multivariate analysis. Results of the multivariate analysis were expressed as odds ratios (OR) and their corresponding confidence intervals (95% CI). The significance threshold was set at 5% ($P < 0.05$).

Table 1a
Patient characteristics ($n = 293$).
Caractéristiques des patients (n = *293*).

	n	(%)
Sex: female	199	68
Age		
≤ 30 years	52	18
> 30 and ≤ 55 years	147	50
> 55 years	94	32
Level of education: higher than high school graduation	147	50
Occupation: executive and senior executive positions, and medical occupations versus other (retired people, unemployed people, students)	37	12
Parent of a child aged ≤ 16 years: yes	114	39
Having a relative working in the healthcare system: yes	121	41
Regular use of the Internet or social networks: yes	206	70
Smoking status: smoker	77	26
Asthma or respiratory failure: yes	36	12
Diabetes: yes	27	9
Consultations with FP		
< 3 times/year versus	54	19
≥ 3 times/year	234	81
Consulting a medical practice – in town (versus in the outskirt)	69	23
Patients presenting with a long-term illness: yes	59	20
Patients benefiting from the universal medical coverage: yes	16	5

FP: family physician.

3. Results

A total of 14 medical practices (78%), out of 18 registered in the region, agreed to take part in the study (3 in the city of Rethel and 11 in the outskirt); 298 questionnaires out of the 350 distributed were filled in. Five of them could not be used for the study purposes. A total of 293 questionnaires were included in the study (83%).

3.1. Epidemiological characteristics of the studied population (Table 1a)

Most participants were female patients (68%). Mean age was 47.4 ± 16.3 years. Overall, 39% of patients had a child aged ≤ 16 years and 50% had achieved a level of education higher than high school graduation. Mean number of consultations per year with the FP was 5.6 ± 4.4. Mean time of follow-up by the medical practice was 13.2 ± 10.1 years.

3.2. Antibiotic therapy: opinion, practice, and sources of information (Table 1b)

Overall, 61% of patients had a positive opinion of antibiotics and 7% had a negative opinion. We observed that 48% of patients had taken antibiotics in the previous 12 months. Self-medication for themselves or for a relative was observed in 13% of patients. The main source of information for bacterial resistance to antibiotics was the media for 81% of patients and the FP for 32%.

3.3. Knowledge of antibiotics (Table 2)

Mean score of correct answers was 5.1 ± 2.7. We observed a 66% rate of correct answers to the statement: "Antibiotics are effective against bacteria". However, patients also believed antibiotics to be effective against viruses and fungal infections (31% and 29%, respectively). Overall, 44% of patients knew that antibiotics were effective against bacteria and ineffective against viruses; 19% also knew that they were ineffective against fungal infections.

Twenty-two per cent of patients thought that antibiotics needed to be prescribed for rhinopharyngitis and 54% for bronchitis or influenza. They also believed antibiotics helped in achieving a quicker recovery, regardless of the infection (45% of cases). Besides, only 27% of patients were aware of the impact of antibiotics on the commensal flora.

Table 1b
Opinion, experience, and sources of information regarding antibiotics and antibiotic resistance ($n = 293$).
Opinion, expérience et sources d'informations concernant les antibiotiques et la résistance bactérienne aux antibiotiques (n = *293*).

	n	(%)
Opinion related to antibiotics		
Positive	178	61
Negative	22	7
No opinion	93	32
Self-medication for antibiotic use: yes (versus no)	39	13
Antibiotic consumption in the previous 12 months		
Yes	140	48
No	133	46
Unknown	18	6
Bacterial resistance to antibiotics		
Relative who contracted an infection caused by a resistant bacterium		
Yes	44	15
No	189	64
Unknown	60	21
Information received by the media: yes (versus no)	238	81
Discussion with the FP: yes (versus no)	94	32

FP: family physician.

3.4. Knowledge of bacterial resistance to antibiotics (Table 2)

Mean score of correct answers was 2.7 ± 1.7. The response rate for "unknown" answers was between 30% and 48% depending on questions. Overall, 65% of patients were aware of the growing epidemiology of highly resistant bacteria worldwide, and 46% knew about the associated risk of death. However, only 26% of patients knew that "resistance to antibiotics decreases with antibiotic prescription reduction".

3.5. Factors associated with antibiotic knowledge (Tables 3, 4a and 4b)

Patient characteristics significantly associated with antibiotic knowledge defined by the previously set criterion (being aware of antibiotic target, i.e. antibiotics are effective against bacteria and ineffective against viruses) or by the criterion related to a score of correct answers $\geq 6/10$, were similar in both univariate analyses: age, sex, level of education, occupation, regular use of the Internet, number of consultations per year with the FP, having been informed by the media, presenting with asthma or respiratory failure, benefiting from the universal medical coverage, not being aware whether or not a relative had contracted an infection caused by a highly resistant bacterium, and not being aware of one's own recent antibiotic consumption (Table 3). Patients aged 55–70 years and > 70 years were grouped together as their scores were similar.

The results of the multivariate analysis revealed that characteristics such as female patients, a level of education higher than high school graduation, the number of consultations per year (< 3), and getting information from the media were significantly associated with good knowledge of antibiotics, defined as being aware of the antibiotic target and by the score of correct answers. However, characteristics such as being aged ≤ 30 years, presenting with respiratory failure or asthma, and not knowing whether or not a relative had contracted a highly resistant bacterial infection were associated with poor knowledge of antibiotics (Tables 4a and 4b). Patients benefiting from the universal medical coverage and belonging to higher occupational categories were also associated with knowledge of antibiotics, as defined by the score of correct answers.

Table 2
Knowledge of antibiotics and antibiotic resistance.
Évaluation de la connaissance des antibiotiques et de la résistance bactérienne aux antibiotiques.

	True *n* (%)	False *n* (%)	Unknown *n* (%)
Antibiotics are effective			
Against bacteria	194 (66)	36 (12)	63 (21)
Against viruses	91 (31)	146 (50)	56 (19)
Against mycosis	85 (29)	90 (31)	118 (40)
In case of a fever, regardless of its origin	60 (20)	184 (63)	49 (17)
In case of a cough, regardless of its origin	54 (18)	195 (67)	44 (15)
In case of fatigue, regardless of its origin	16 (5)	225 (77)	52 (18)
Antibiotics help recover			
More rapidly from an infection, regardless of its cause	131 (45)	115 (39)	47 (16)
From rhinopharyngitis	65 (22)	189 (64)	39 (13)
From bronchitis or influenza	159 (54)	87 (30)	47 (16)
Antibiotics are ineffective against bacteria that are naturally present in humans (skin and digestive tube)	52 (18)	79 (27)	162 (55)
Bacterial resistance to antibiotics			
Bacterial resistance to antibiotics decreases if antibiotic prescriptions are reduced	75 (26)	93 (32)	124 (42)
Bacterial resistance to antibiotics is a problem strictly limited to hospital or nursing home settings	12 (4)	174 (60)	106 (36)
Antibiotic resistance is not important because new antibiotics are regularly being discovered	56 (19)	101 (35)	135 (46)
The prevalence of bacteria highly resistant to antibiotics are increasing worldwide	190 (65)	13 (4)	89 (30)
Bacteria resistant to antibiotics can be transmitted to someone who has not received any antibiotics	108 (37)	63 (22)	121 (41)
Bacteria resistant to all antibiotics have already been the cause of deaths	135 (46)	17 (6)	140 (48)

Table 3
Factors associated with knowledge of antibiotics and antibiotic resistance–univariate analysis.
Facteurs associés à la connaissance des antibiotiques et de la résistance des bactéries aux antibiotiques – analyse univariée.

Factors	Antibiotic target	OR (95% CI)	*P*	ATB score	OR (95% CI)	*P*	R score	OR (95% CI)	*P*
Sex									
Male	34	1		37	1		56	1	
Female	49	1.88 (1.12–3.12)	0.014	54	2.00 (1.21–3.30)	0.006	52	0.84 (0.51–1.38)	0.51
Age									
≤ 30 years	35	0.44 (0.22–0.85)	0.001	40	0.46 (0.24–0.88)	0.01	50	0.75 (0.39–1.41)	0.37
> 30 and ≤ 55 years	54	1		59	1	9	57	1	
> 55 years	34	0.43 (0.25–0.73)	0.001	37	0.40 (0.24–0.69)	< 0.001	50	0.75 (0.44–1.26)	0.27
Level of education									
Higher than high school graduation	62	4.45 (2.71–7.31)	< 0.001	69	5.43 (3.29–8.96)	0.001	65	2.47 (1.54–3.96)	< 0.001
Lower than high school graduation	27	1		29	1		42	1	
Executive and senior executive positions, and medical occupations	73	4.01 (1.86–8.63)	< 0.001	83	6.64 (2.67–16.47)	< 0.001	73	2.61 (1.21–5.26)	0.01
Versus other occupations	40	1		44	1		51	1	
Parent of a child aged ≤ 16 years									
Yes	51	1.53 (0.95–2.47)	0.07	55	1.52 (0.95–2.45)	0.08	52	0.88 (0.55–1.41)	0.62
No	40	1		45	1		55	1	
Having a relative working in the healthcare system									
Yes	48	1.27 (0.80–2.04)	0.30	51	1.18 (0.74–1.88)	0.48	56	1.19 (0.74–1.90)	0.45
No	42	1		47	1		52	1	
Regular use of the Internet									
Yes	50	2.48 (1.45–4.26)	< 0.001	57	3.46 (2.00–5.98)	< 0.001	55	1.21 (0.73–2.01)	0.45
No	29	1		28	1		50	1	
Information received from the media									
Yes	50	3.52 (1.77–7.01)	< 0.001	55	4.38 (2.20–8.73)	< 0.001	59	3.54 (1.87–6.69)	< 0.001
No	22	1		22	1		29	1	
Information received by the family physician									
Yes	44	0.95 (0.58–1.56)	0.86	48	0.94 (0.57–1.54)	0.83	60	1.42 (0.87–2.35)	0.16
No	45	1		49	1		51	1	
Smoking status									
Smoker	40	0.80 (0.47–1.36)	0.42	42	0.67 (0.40–1.14)	0.15	53	0.97 (0.57–1.63)	0.91
Non-smoker	46	1		51	1		54	1	
Presenting with diabetes									
Yes	33	0.59 (0.25–1.38)	0.22	30	0.40 (0.17–0.96)	0.036	48	0.78 (0.35–1.73)	0.55
No	45	1		51	1		54	1	

Table 3 (*Continued*)

Factors	Antibiotic target	OR (95% CI)	*P*	ATB score	OR (95% CI)	*P*	R score	OR (95% CI)	*P*
Presenting with respiratory failure or asthma									
Yes	17	0.21 (0.08–0.53)	< 0.001	22	0.25 (0.11–0.58)	< 0.001	50	0.84 (0.42–1.70)	0.64
No	48	1		52	1		54	1	
Presenting with a long-term illness									
Yes	34	0.57 (0.31–1.05)	0.07	37	0.55 (0.30–0.99)	0.047	54	1.03 (0.58–1.83)	0.91
No	47	1		52	1		53	1	
Benefiting from the universal medical coverage									
Yes	12	0.16 (0.03–0.74)	0.006	6	0.06 (0.01–0.48)	< 0.001	56	1.12 (0.40–3.11)	0.81
No	46	1		51	1		53	1	
Consulting a medical practice in town									
Yes	39	0.75 (0.43–1.30)	0.32	48	0.95 (0.55–1.63)	0.85	49	0.79 (0.46–1.36)	0.41
No	46	1		49	1		55	1	
Self-medication									
Yes	51	1.37 (0.70–2.70)	0.35	49	0.99 (0.50–1.95)	0.99	51	0.89 (0.45–1.76)	0.76
No	43	1		49	1		54	1	
Number of consultations per year									
< 3	63	2.53 (1.37–4.66)	0.002	68	2.72 (1.44–14.82)	0.001	54	1.01 (0.55–1.83)	0.97
> 3	40	1		44	1		53	1	
Number of years consulting the same medical practice									
< 3 years	38	0.73 (0.40–1.36)	0.33	47	0.96 (0.53–1.75)	0.91	60	1.43 (0.78–2.63)	0.24
≥ 3 years	45	1		48	1		51	1	
Recent antibiotic consumption									
Yes	48	4.21 (1.16–15.19)	0.018	48	4.58 (1.27–16.55)	0.002	55	9.77 (2.16–44.1)	< 0.001
No	46	4.36 (1.20–15.79)	0.016	54	5.90 (1.63–21.34)	0.002	59	11.34 (2.50–51.35)	< 0.001
Unknown	17	1		17	1		11	1	
Opinion related to antibiotics									
Positive	48	1.51 (0.90–2.52)	0.11	52	1.54 (0.93–2.57)	0.09	57	1.77 (1.07–2.95)	0.02
Negative	45	1.38 (0.54–3.52)	0.49	59	2.09 (0.81–5.37)	0.12	68	2.83 (1.65–7.61)	0.03
No opinion	38	1		41	1		43	1	
Relative who contracted an infection caused by a resistant bacterium									
Yes	54	3.94 (1.69–9.15)	0.001	57	3.94 (1.71–9.09)	< 0.001	64	2.81 (1.25–6.29)	0.01
No	49	3.11 (1.60–6.04)	< 0.001	54	3.59 (1.87–6.88)	< 0.001	59	2.05 (1.13–3.72)	0.02
Unknown	23	1		25	1		38	1	

R score: score related to knowledge of bacterial resistance to antibiotics.

Table 4a
Factors associated with knowledge of antibiotics (knowledge of the target) – multivariate analysis.
Facteurs associés aux connaissances sur les antibiotiques (connaissance de la cible des antibiotiques) – analyse multivariée.

	OR	95% CI	*P*
Age: > 30 and ≤ 55 versus ≤ 30 years	2.63	1.17–5.88	0.018
> 30 and ≤ 55 versus > 55 years	0.95	0.46–1.94	0.890
Recent antibiotic consumption: unknown versus yes and no	0.55	0.12–2.42	0.432
Higher than high school graduation	4.06	2.11–7.81	< 0.001
Benefiting from the universal medical coverage	0.40	0.07–2.25	0.215
Presenting with respiratory failure or asthma	0.19	0.06–0.61	0.003
Information on bacterial resistance to antibiotics received from the media	3.04	1.35–6.83	0.006
Relative who contracted an infection caused by a resistant bacterium: unknown versus yes and no	0.36	0.16–0.78	0.010
Occupation: executive and senior executive positions, and medical occupations versus other	2.31	0.91–5.81	0.076
Regular use of the Internet or social networks	1.22	0.58–2.53	0.590
Sex (women vs men)	2.69	1.40–5.16	0.002
Consultation with the family physician: < 3 versus ≥ 3 per year	2.80	1.27–6.17	0.010

Table 4b
Factors associated with knowledge of antibiotics (score ≥ mean) – multivariate analysis.
Facteurs associés aux connaissances sur les antibiotiques (score supérieur à la moyenne) – analyse multivariée.

Factors	OR	95% CI	*P*
Age: > 30 and ≤ 55 versus ≤ 30 years	2.93	1.24–6.88	0.013
> 30 and ≤ 55 versus > 55 years	0.91	0.41–1.98	0.813
Recent antibiotic consumption: unknown versus yes and no	0.46	0.10–2.18	0.334
Higher than high school graduation	5.44	2.70–10.96	< 0.001
Benefiting from the universal medical coverage	0.10	0.01–0.96	0.046
Presenting with a long-term illness	1.27	0.49–3.26	0.614
Presenting with diabetes	1.47	0.39–5.55	0.561
Presenting with respiratory failure or asthma	0.21	0.07–0.61	0.004
Information on resistance to antibiotics received from the media	4.62	1.95–10.92	< 0.001
Having a relative who contracted an infection caused by a resistant bacterium: unknown versus yes and no	0.28	0.12–0.65	0.002
Occupation: executive and senior executive positions, and medical occupations versus other	3.27	1.08–10.17	0.035
Regular use of the Internet or social networks	1.86	0.86–4.02	0.109
Sex (women vs male)	3.60	1.77–7.29	< 0.001
Consultation with the family physician: < 3 versus ≥ 3 per year	3.55	1.46–8.60	0.005

3.6. Factors associated with knowledge of bacterial resistance to antibiotics (Tables 3 and 4c)

The results of the multivariate analysis revealed that patient characteristics associated with good knowledge of bacterial resistance to antibiotics were a level of education higher than high school graduation, belonging to higher occupational categories, getting information from the media, and having a specific opinion about antibiotics – positive or negative versus no opinion. Not knowing whether or not one had received antibiotics was associated with poor knowledge of bacterial resistance to antibiotics.

4. Discussion

We conducted the study from 2014 to 2015 in Rethel, a small city in the North-East of France, and its outskirt. Our study results show that knowledge of antibiotics (target and relation between consumption and emergence of bacterial resistance) is suboptimal.

4.1. Knowledge of antibiotic target and indications

Only 66% of patients answered correctly to the statement: "Antibiotics can be used to treat bacterial infections". This figure is similar to that observed in the United States in 2003 (66%) as well as in a meta-analysis of 65% of studies conducted in western countries between 2000 and 2013 (66%) [18,19].

To the statement: "Antibiotics are effective against viruses", 50% of interviewed individuals declared not to be aware of the answer. This percentage is quite similar to that observed in the same above-mentioned meta-analysis (54%), but it is higher that the European average estimated at 40% in the 2013 Eurobarometer – a European study aiming at evaluating antibiotic consumption and knowledge of antibiotics [19,20]. It must however be noted that, in the Eurobarometer, French individuals answered correctly in 59% of cases. Geographical differences related to knowledge of antibiotics could explain this lack of harmony. Thus, the results of a study conducted in Grenoble in 2012 showed that only 25% of interviewed individuals answered incorrectly [21].

Table 4c
Factors associated with knowledge of antibiotic resistance – multivariate analysis.
Facteurs associés aux connaissances sur la résistance des bactéries aux antibiotiques – analyse multivariée.

	OR	95% CI	*P*
Recent antibiotic consumption: unknown versus yes and no	0.14	0.02–0.68	0.015
Higher than high school graduation	1.72	1.03–2.89	0.038
Information on bacterial resistance to antibiotics received from the media	3.11	1.58–6.12	0.001
Opinion related to antibiotics: positive and negative opinion versus no opinion	1.92	1.11–3.29	0.018
Relative who contracted an infection caused by a resistant bacterium: unknown versus yes and no	0.58	0.30–1.09	0.093
Occupation: executive and senior executive positions, and medical occupations versus other	2.37	1.00–5.60	0.049

The target of antibiotics was only known by 44% of individuals. The action of antibiotics on bacteria alone is thus far from being known by the general population. The lack of precision for the term "antibiotic" might explain this high figure. Using the term "antibacterial" might help patients clearly understand the role of these drugs.

The absence of antibiotic indication for rhinopharyngitis is known by 64% of patients; this figure is similar to the French score observed in the 2013 Eurobarometer (64%) [20]. Nevertheless, the percentage of incorrect answers has not improved over time: 22% in 2002 and 22% in our study [7].

Answers related to antibiotic effectiveness in case of bronchitis or influenza are far from being optimal, with 70% of incorrect answers, while bronchitis is the first viral cause of antibiotic consumption in France. More than three-quarters of bronchitis case patients are indeed treated with antibiotics [4]. This disappointing score is, however, close to that observed in other studies: 67% in an Austrian study published in 2013 [22], and 92%, 88%, and 74% in three American studies published in 2003 and 2005 [18,23,24]. Similarly, 92% of interviewed individuals in Norway in 2009 thought that bronchitis with yellowish expectoration had to be treated with an antibiotic therapy [25].

4.2. Knowledge of bacterial resistance to antibiotics

Most patients had already heard about bacterial resistance to antibiotics in the media (81%), knew that it was a growing problem worldwide (65%), and that it was not restricted to hospital or nursing home settings (60%). In the 2013 Eurobarometer, 85% of French respondents answered correctly to the statement: "The excessive consumption of antibiotics leads to their inefficacy". However, only 26% of our study population was aware of the relation between bacterial resistance and antibiotic overconsumption. This discrepancy could be due to the lack of clarity of the Eurobarometer statement compared with ours, i.e. "Resistance to antibiotics decreases if antibiotic prescriptions are reduced". The transmission mode of resistant bacteria is also poorly known; 37% of our study participants did not know that bacteria resistant to antibiotics could be transmitted to someone who had not taken any antibiotics. Unlike a study conducted in Greece in 2011 (50%), very few people (19%) believed the launch of new antibiotics could solve the issue of bacterial resistance [26].

4.3. Population at risk of limited knowledge related to antibiotics

4.3.1. Men

In our study, as well as in others, women had better knowledge of antibiotics than men, regardless of their occupation or level of education [13,20,22,27,28]. We noticed that mothers are more likely to take their child to the physician's office than fathers [21,25,29,30]. Also, the consumption of antibiotics among women is higher than in men, mainly because of a higher incidence of cystitis. Both of these factors could partly explain women's better knowledge of antibiotics as compared with men [3,20].

4.3.2. Individuals with a level of education lower than high school graduation

Similar to the results of various studies, the level of education is also an independent factor associated with knowledge of antibiotics and of bacterial resistance to antibiotics [13,14,20,22,23,27–29,31]. In the 2013 Eurobarometer, 32% of interviewed individuals who had completed their studies at 20 years old or above answered correctly to all questions, versus only 14% of individuals who had dropped out of school after 15 years old or below [20]. It would therefore be interesting to make pupils and students aware of antibiotic resistance issues as early as secondary school.

4.3.3. Individuals aged below 30 years

Our study results indicate that younger people are more likely to know less about antibiotics than older individuals, as observed in other studies [7,18,22,28]. However, the results of some studies indicated that younger people obtained better scores [14,20,29]. This could be explained by the differences across countries and by the age limit used.

4.4. Patients presenting with respiratory failure or asthma

Poor knowledge of antibiotics was observed in patients presenting with respiratory failure and/or asthma. This population has never been studied in similar studies. As the use of antibiotics [32] may sometimes be required for bronchitis, even when a viral origin is suspected, it may have given these patients the wrong impression about the use of antibiotics in this situation.

4.5. Occupation

We observed that the category "executive and senior executive positions, and medical occupations" was an independent factor associated with good knowledge of antibiotics. Other studies did not assess the occupation criterion as a variable, but rather focused on income. A positive association was thus observed between high income and good knowledge [14,20]. Thus, in the 2013 Eurobarometer, a quarter of interviewed individuals who almost never had any difficulties in paying their bills answered correctly to the questions, versus 16% of people who found it most often difficult to pay their bills [20]. The authors of an English study conducted in 2007 observed that a poor social background and poor knowledge of antibiotics were associated (OR 4.9, 95% CI 3.5–6.3, $P < 0.001$) [13]. We observed, in our study, that benefiting from the universal medical coverage was also an independent factor associated with poor knowledge of antibiotics as defined by the score obtained at the questionnaire.

4.6. Sources of information – impact of the media

In 2013, France was the first European country in terms of information received by patients on antibiotics, with 65% of French people declaring to have learned about antibiotics in the media in the previous 12 months [20]. This was also confirmed in our study, with 80% of respondents having received at least one piece of information from the media. The conveyed information is also an independent factor in terms of knowledge of antibiotics and of bacterial resistance to antibiotics. The impact of these media campaigns was also observed in the 2013 Eurobarometer, with a positive relation between the level of knowledge related to antibiotics and being told not to make an excessive use of them. Among people informed about antibiotics, 62% of those with good knowledge mentioned the media as their source of information versus 45% of those with poor knowledge [20]. Access to the Internet and social networks was not associated with good knowledge of antibiotics in our study. Knowledge of antibiotics thus depends on the implementation of active educational measures using media campaigns.

Paradoxically, family physicians were rarely the source of information (32%) in our study, and are not associated with good knowledge of antibiotics. This result is similar to the one observed in the 2013 Eurobarometer: only 26% of interviewed people with good knowledge had been informed by healthcare professionals versus 44% of those with poor knowledge. Findings from an Austrian study conducted in 2010–2011 showed that people mentioning the media or the Internet as their source of information also got a better score than those declaring to get information from their family physician. However, family physicians were the main source of information for patients with a low level of education [22]. The same was observed in the 2013 Eurobarometer: people who had dropped out of school early were more likely to get informed by their FP than those with a higher level of education (41% versus 28%).

The opposite relation was, however, observed in our study for antibiotic knowledge and the number of yearly consultations with the FP. Also, a higher number of consultations was associated with an excessive consumption of antibiotics. Family physicians should therefore be made aware of their educational role with people considered at risk in this study.

4.7. Strengths and limitations

Our study participation rates were 78% for family physicians and 83% for patients. Our sample ($n = 293$) was representative of patients consulting in general medicine, with a higher number of female patients (68%) [21,25,29,30] and a similar percentage of patients presenting with a long-term illness than those observed at the department (Ardennes) level in 2008 (20% versus 19%) [33]. Forty-eight per cent of patients declared to have received an antibiotic treatment in the previous 12 months. This percentage is similar to that observed in the 2013 Eurobarometer (44%), the European average being 35% [20]. However, this figure may be partly overestimated because of incorrect answers given by some patients, due to their poor knowledge of this drug class.

Thirteen per cent of patients declared to have already self-medicated themselves or a relative with antibiotics. This figure is similar to the 12% figure observed in France in 2002 [7]. However, a lower figure was observed for patients benefiting from the universal medical coverage: 5% versus 10.4% in 2014 in the Ardennes department [33,34]. Besides, the percentage of immigrant patients has not been assessed in our study, but language barrier has never been an issue for completing questionnaires.

5. Conclusion

Despite the positive impact of awareness campaigns on patient education, knowledge of antibiotics remains rather poor overall. Only a quarter of patients know that reducing antibiotic consumption is one of the means to fight against bacterial resistance. Media campaigns should therefore be intensified and should better highlight the relation between bacterial resistance and antibiotic consumption. Healthcare professionals and family physicians should help improve knowledge of antibiotics among poorly informed people (men, young people, and individuals from a poor social and cultural background). Explicative posters and patient evaluation questionnaires with information provided by family physicians should be considered.

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Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Agence nationale de sûreté du médicament (ANSM). L'évolution des consommations. d'antibiotiques en France entre 2000 et 2013 [Internet]; 2015 http://ansm.sante.fr/content/download/69355/884959/version/1/file/ANSM_rapport_consommation_antibio+2013.pdf.

[2] Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, et al. European surveillance of antimicrobial consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). J Antimicrob Chemother 2011;66(Suppl. 6):vi3–12.

[3] Agence nationale de sûreté du médicament (ANSM). Dix ans d'évolution. Des consommations d'antibiotiques en France [Internet]; 2015 http://www.ansm.sante.fr/content/download/34203/447730/version/5/file/Rapport-Consommation-Antibiotiques-1999-2009.pdf.

[4] Caisse nationale de l'assurance maladie des travailleurs salariés (CNAMTS). Dossier de presse. Antibiotiques : où en est-on ? [Internet]; 2015 http://www.puppem.com/documents/cnamts_dp_antibiotiques_05-2010.pdf.

[5] De Saint-Hardouin G, Goldgewicht M, Kemeny G, Rufat P, Perronne C. Évaluation de la pression des parents sur les médecins pour la prescription des antibiotiques dans les infections ORL de l'enfant en ville. Med Mal Infect 1997;27(4):372–8.

[6] Attali C, Rola S, Renard V, Roudot-Thoraval F, Montagne O, Le Corvoisier P, et al. Situations cliniques à risque de prescription non conforme aux recommandations et stratégies pour y faire face dans les infections respiratoires présumées virales. Exercer 2008;82:66–72.

[7] Caisse nationale de l'assurance maladie des travailleurs salariés (CNAMTS), Ipsos. Regards croisés médecins/patients sur les antibiotiques. Conférence de presse [Internet]; 2015 http://ars.sante.fr/fileadmin/MIDI-PYRENEES/2_BON_USAGE/Fichiers/ANTIBIOS_SyntheseIPSOS_2002.pdf.

[8] Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis 2014;14:13.

[9] Organisation mondiale de la santé (OMS). Communiqué de presse. Premier rapport de l'OMS sur la résistance aux antibiotiques : une menace grave d'ampleur mondiale [Internet]; 2015 http://www.who.int/mediacentre/news/releases/2014/amr-report/fr/.

[10] Wang S, Pulcini C, Rabaud C, Boivin JM, Birgé J. Inventory of antibiotic stewardship programs in general practice in France and abroad. Med Mal Infect 2015;45(4):111–23, http://dx.doi.org/10.1016/j.medmal.2015.01.011 [Epub 2015 Mar 5].

[11] Giry M, Pulcini C, Rabaud C, Boivin JM, Mauffrey V, Birgé J. Acceptability of antibiotic stewardship measures in primary care. Med Mal Infect 2016, http://dx.doi.org/10.1016/j.medmal.2016.02.001 [Epub ahead of print, pii: S0399-07716)00033-0].

[12] Price EL, Mackenzie TD, Metlay JP, Camargo CA, Gonzales R. A computerized education module improves patient knowledge and attitudes about appropriate antibiotic use for acute respiratory tract infections. Patient Educ Couns 2011;85(3):493–8.

[13] McNulty CAM, Boyle P, Nichols T, Clappison P, Davey P. Don't wear me out – the public's knowledge of and attitudes to antibiotic use. J Antimicrob Chemother 2007;59(4):727–38.

[14] Kim SS, Moon S, Kim EJ. Public knowledge and attitudes regarding antibiotic use in South Korea. J Korean Acad Nurs 2011;41(6):742–9.

[15] Finkelstein JA, Huang SS, Kleinman K, Rifas-Shiman SL, Stille CJ, Daniel J, et al. Impact of a 16-community trial to promote judicious antibiotic use in Massachusetts. Pediatrics 2008;121(1):e15–23.

[16] Institut national de la statistique et des études économiques (INSEE) [Internet] Chiffres clés : arrondissement de Rethel (082); 2015 http://www.insee.fr/fr/themes/comparateur.asp?codgeo=arr-082#telechargement.

[17] Institut national de la statistique et des études économiques (INSEE) [Internet] Définitions et méthodes - PCS 2003 - Niveau 1 - Liste des catégories socioprofessionnelles agrégées; 2015 http://insee.fr/fr/methodes/default.asp?page=nomenclatures/pcs2003/liste_n1.htm.

[18] Kuzujanakis M, Kleinman K, Rifas-Shiman S, Finkelstein JA. Correlates of parental antibiotic knowledge, demand, and reported use. Ambul Pediatr 2003;3(4):203–10.

[19] Gualano MR, Gili R, Scaioli G, Bert F, Siliquini R. General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2015;24(1):2–10.

[20] Commission Européenne. Eurobaromètre spécial 407. La résistance aux antimicrobiens [Internet]; 2015 http://ec.europa.eu/public_opinion/archives/ebs/ebs_407_fr.pdf.

[21] Collomb-Gery A [Thèse d'exercice] Évolution des connaissances et habitudes des patients liées à l'antibiothérapie : arguments pour améliorer la prescription en médecine générale. Grenoble: Médecine Générale; 2012.

[22] Hoffmann K, Ristl R, Heschl L, Stelzer D, Maier M. Antibiotics and their effects: what do patients know and what is their source of information? Eur J Public Health 2014;24(3):502–7.

[23] Friedman JF, Lee GM, Kleinman KP, Finkelstein JA. Acute care and antibiotic seeking for upper respiratory tract infections for children in day care: parental knowledge and day care center policies. Arch Pediatr Adolesc Med 2003;157(4):369–74.

[24] Corbett KK, Gonzales R, Leeman-Castillo BA, Flores E, Maselli J, Kafadar K. Appropriate antibiotic use: variation in knowledge and awareness by hispanic ethnicity and language. Prev Med 2005;40(2):162–9.

[25] Filipetto FA, Modi DS, Weiss LB, Ciervo CA. Patient knowledge and perception of upper respiratory infections, antibiotic indications and resistance. Patient Prefer Adherence 2008;2:35–9.

[26] Panagakou SG, Spyridis N, Papaevangelou V, Theodoridou KM, Goutziana GP, Theodoridou MN, et al. Antibiotic use for upper respiratory tract infections in children: a cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. BMC Pediatr 2011;11:60.

[27] André M, Vernby A, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. J Antimicrob Chemother 2010;65(6):1292–6.

[28] Rousounidis A, Papaevangelou V, Hadjipanayis A, Panagakou S, Theodoridou M, Syrogiannopoulos G, et al. Descriptive study on parents' knowledge, attitudes and practices on antibiotic use and misuse in children with upper respiratory tract infections in Cyprus. Int J Environ Res Public Health 2011;8(8):3246–62.

[29] Shlomo V, Adi R, Eliezer K. The knowledge and expectations of parents about the role of antibiotic treatment in upper respiratory tract infection – a survey among parents attending the primary physician with their sick child. BMC Fam Pract 2003;4:20.

[30] Assathiany R, Kemeny J, Sznajder M, Hummel M, Van Egroo LD, Chevallier B. La salle d'attente du pédiatre : lieu d'éducation pour la santé ? Arch Pediatr 2005;12(1):10–5.

[31] Napolitano F, Izzo MT, Di Giuseppe G, Angelillo IF. Public knowledge, attitudes, and experience regarding the use of antibiotics in Italy. Plos One 2013;8(12):e84177.

[32] Azria R, Barry B, Bingen E, Cavallo J-D, Chidiac C, Francois M, et al. Antibiotic stewardship. Med Mal Infect 2012;42(10):460–87.

[33] Fonds de financement de la protection complémentaire de la couverture universelle du risque maladie. Annuaire Statistique [Internet]. http://www.cmu.fr/fichier-utilisateur/fichiers/Annuaire_Statistique_11_2014.pdf (accessed on August 9, 2015).

[34] Plates-formes d'appui aux professionnels de santé (PAPS) Champagne-Ardenne. La santé dans la région Champagne-Ardenne: Indicateurs régionaux. [Internet]. http://www.champagne-ardenne.paps.sante.fr/fileadmin/CHAMPAGNE-ARDENNE/PAPS/Choix_d_mode_d_exercice/Fiches_sante_ORS/4_Morbidite_et_determinants_sante.pdf (accessed on August 9, 2015).

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Original article

In vitro activity of ceftobiprole on 440 *Staphylococcus aureus* strains isolated from bronchopulmonary infections

Activité in vitro du céftobiprole sur 440 souches de Staphylococcus aureus *isolées d'infections broncho-pulmonaires en France*

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Abstract

Objective. – We assessed the in vitro activity of ceftobiprole on 440 *Staphylococcus aureus* clinical strains isolated from bronchopulmonary infections (2010–2014).

Methods. – *S. aureus* isolates were characterized for methicillin resistance, PVL status, and clonal complex. All isolates were tested for minimal inhibitory concentrations (MIC) determination by broth microdilution method for ceftobiprole, ceftaroline fosamil, and comparator antibiotics (linezolid, tigecycline, vancomycin, and daptomycin).

Results. – A total of 325 (74%) strains were methicillin-susceptible *S. aureus* (MSSA) and 115 (26%) were methicillin-resistant *S. aureus* (MRSA); 105 (24%) *S. aureus* strains were PVL-positive, including 35.2% (37/105) MRSA and 64.8% (68/105) MSSA. Ceftobiprole was highly active against *S. aureus* with MIC_{90} of 1 mg/L, MICs ranging between 0.12 and 4 mg/L (only one resistant strain, MIC of 4 mg/L). MIC_{50} and MIC_{90} were twice lower in MSSA than MRSA. Moreover, PVL^+ MRSA were slightly more susceptible to ceftobiprole (MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L) than PVL^- MRSA (MIC_{50} and MIC_{90} of 1 mg/L). The ceftobiprole-resistant strain was also resistant to ceftaroline fosamil and presented the D239L mutation in PBP2A. The comparator antibiotics were equally active on the strains tested, with MIC_{90} of 0.5 mg/L for ceftaroline fosamil, tigecycline, and daptomycin; 1 mg/L for vancomycin; and 2 mg/L for linezolid.

Conclusions. – Our results suggest that ceftobiprole is highly active against *S. aureus* and is an effective alternative to vancomycin or linezolid in the management of staphylococcal pneumonia. However, close monitoring of isolates should be maintained to prevent resistant strain diffusion.

Keywords: Ceftaroline fosamil; Ceftobiprole; Bronchopulmonary infections; *Staphylococcus aureus*

Résumé

Objectifs. – Nous avons testé l'activité in vitro du céftobiprole sur une série française de 440 souches de *Staphylococcus aureus*, toutes isolées d'infections broncho-pulmonaires entre 2010 et 2014.

Méthodes. – Nous avons utilisé une méthode par microdilution pour déterminer les concentrations minimales inhibitrices (CMI) de céftobiprole, céftaroline, linézolide, tigécycline, vancomycine et daptomycine, et avons recherché la résistance à la méticilline et le portage de la PVL.

Résultats. – Nous avons recensé 325 (74 %) *S. aureus* sensibles à la méticilline (SASM), 115 (26 %) résistants (SARM) et 105 porteurs de la PVL, dont 68 SASM et 37 SARM. Le céftobiprole était très actif sur *S. aureus*, avec une CMI_{90} de 1 mg/L. Une seule souche était résistante avec une CMI de 4 mg/L, également résistante à la céftaroline. Les SARM présentaient des CMI_{50} et CMI_{90} au céftobiprole deux fois supérieures à

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celles des SASM. Les SARM porteurs de la PVL y étaient légèrement plus sensibles que les SASM non porteurs (CMI_{50} à 0,5 mg/L et 1 mg/L, respectivement). Les autres antibiotiques anti-staphylococciques testés étaient également actifs sur *S. aureus*, avec des CMI_{90} à 0,5 mg/L pour céftaroline, tigécycline et daptomycine, 1 mg/L pour vancomycine et 2 mg/L pour linézolide.

Conclusions. – Le céftobiprole est très actif sur *S. aureus* et constitue une bonne alternative à la vancomycine ou au linézolide dans les pneumopathies staphylococciques. Cependant, il est important de suivre l'évolution de cette sensibilité au cours du temps afin de détecter l'émergence et la diffusion des souches résistantes.

Mots clés : Céftaroline ; Céftobiprole ; Infections broncho-pulmonaires ; *Staphylococcus aureus*

1. Introduction

Ceftobiprole medocaril is the prodrug form of ceftobiprole, a new subclass of cephalosporin with an activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria. Just like other β-lactams, ceftobiprole blocks peptidoglycan cell wall synthesis by binding to penicillin-binding proteins (PBPs). The peculiar characteristic of ceftobiprole is its high affinity for PBP2a, involved in methicillin resistance of *S. aureus*. Ceftobiprole has recently been approved in Europe for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) (excluding ventilator-associated pneumonia) in adults, where the incriminating pathogens are multidrug-resistant [1].

S. aureus is a major pathogen in humans, responsible for various types of infections, including pneumonia [2]. In France, *S. aureus* pneumonia accounts for 12.6% of CAP [3] and a large proportion of HAP [4]. An early effective treatment is essential for *S. aureus* pneumonia management, and affects patient outcomes [5]. Moreover, some *S. aureus* strains producing Panton-Valentine leukocidin (PVL) can induce life-threatening necrotizing pneumonia, which urgently requires both bactericidal and antitoxin treatment against *S. aureus* [6].

Several studies have shown that ceftobiprole was very effective against pathogens isolated from hospitalized patients, including *S. aureus* and MRSA [7–10]. Nevertheless, it is essential to monitor the antimicrobial activity of ceftobiprole on bacteria involved in bronchopulmonary infection (which is the on-label indication of ceftobiprole), and notably on *S. aureus* and MRSA isolated in a country-specific setting, to detect potential changes in susceptibility pattern.

We aimed to study the in vitro activity of ceftobiprole on 440 *S. aureus* clinical strains, all isolated from bronchopulmonary infections in French patients between 2010 and 2014. *S. aureus* isolates were characterized for methicillin resistance, PVL status, and clonal complex (CC) to then analyze the susceptibility to ceftobiprole in various *S. aureus* genotypes.

2. Materials and methods

2.1. Bacterial strains

A total of 440 *S. aureus* strains were selected among French Staphylococci National Reference Center (Staphylococci NRC, Lyon, France) collections from 2010 to 2014. All *S. aureus* strains were isolated from respiratory infections, in French clinical laboratories, and sent to the Staphylococci NRC, either because of clinical severity of symptoms or because of particular antibiotic resistance patterns. Thirty-three per cent of *S. aureus* strains were isolated from tracheal aspirates, 26% from bronchoalveolar lavage fluid, 20% from sputum (including 8% from cystic fibrosis patients), 9% from pleural effusion, 8% from blood culture during pneumonia, and 4% from lung biopsy and abscesses. Species identification was confirmed at the Staphylococci NRC by MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization-Time of Light) mass spectrometry, VitekMS (BioMérieux®). *S. aureus* strains were stored at –20 °C. All isolates were characterized using *S. aureus* Genotyping Kit 2.0 Alere Technologies GmbH (Jena, Germany). When needed, the *mecA* gene was sequenced as previously described [11].

2.2. Susceptibility testing method

All isolates were tested for minimal inhibitory concentration (MIC) determination by broth microdilution method using validated commercially prepared panels, Sensititre Trek Diagnostic Systems, Life Technologies Europe (Naerum, Denmark), in Mueller-Hinton broth for ceftobiprole, ceftaroline fosamil, and comparator antimicrobial agents (linezolid, tigecycline, vancomycin, and daptomycin). Susceptibility interpretation was based on EUCAST breakpoints [12].

3. Results

3.1. Epidemiological distribution of S. aureus strains isolated from bronchopulmonary infections

Among the 440 *S. aureus* strains isolated from bronchopulmonary infections, 325 (74%) were methicillin-susceptible *S. aureus* (MSSA) and 115 (26%) were methicillin-resistant *S. aureus* (MRSA), based on *mecA* gene presence. No *mecC* was detected among all selected strains. With regard to PVL status, 105 (24%) *S. aureus* strains carried *luk-PV* gene, 35.2% were MRSA strains (37/105) whilst 64.8% (68/105) were MSSA strains.

With regard to the genetic background, 216 strains (49.9%) belong to the agr1 group, 106 strains (24.5%) to agr2, 91 strains (21.0%) to agr3, and 20 strains (4.6%) to the agr4 group. Overall, *S. aureus* clustered within 26 clonal complexes; most isolates clustered into the CC8 (69/440, 15.7%), CC5 (61/440, 13.9%),

Table 1
Molecular characterization of *S. aureus* strains isolated from bronchopulmonary infections in France, from 2010 to 2014.
Caractérisation moléculaire des souches de S. aureus *isolées d'infections broncho-pulmonaires en France, entre 2010 et 2014.*

Clonal complex	Agr group	*mecA*	PVL	Number (% of total)	Number (% of total) of clonal complex
8	1	–	–	23 (5.2)	69 (15.7)
			+	1 (0.2)	
		+	–	38 (8.6)	
			+	7 (1.6)	
5	2	–	–	38 (8.6)	61 (13.9)
			+	5 (1.1)	
		+	–	15 (3.4)	
			+	3 (0.7)	
30	3	–	–	31 (7.0)	41 (9.3)
			+	8 (1.8)	
		+	+	2 (0.5)	
398	1	–	–	35 (8.0)	36 (8.2)
			+	1 (0.2)	
15	2	–	–	19 (4.3)	26 (5.9)
			+	7 (1.6)	
45	1, 4	–	–	22 (5.0)	23 (5.2)
		+	–	1 (0.2)	
121	2, 4	–	–	4 (0.9)	20 (4.5)
			+	16 (3.6)	
80	3	+	+	16 (3.6)	18 (4.1)
		–	+	2 (0.5)	
1	3	–	–	7 (1.6)	17 (3.9)
			+	5 (1.1)	
		+	–	5 (1.1)	
152	1	–	+	16 (3.6)	16 (3.6)
22	1	–	–	8 (1.8)	14 (3.2)
			+	2 (0.5)	
		+	–	4 (0.9)	
59	1	–	–	8 (1.8)	11 (2.5)
		+	–	2 (0.5)	
			+	1 (0.2)	
7	1	–	–	7 (1.6)	7 (1.6)
97	1	–	–	5 (1.1)	6 (1.4)
		+	–	1 (0.2)	
88	3	+	+	4 (0.9)	5 (1.1)
		+	–	1 (0.2)	
9	2	–	–	5 (1.1)	5 (1.1)
12	2	–	–	5 (1.1)	5 (1.1)
20	1	–	–	4 (0.9)	4 (0.9)
25	1	–	–	4 (0.9)	4 (0.9)
188	1	–	–	4 (0.9)	4 (0.9)
6	1	+	–	2 (0.5)	3 (0.7)
		–	+	1 (0.2)	
101	1	–	–	3 (0.7)	3 (0.7)
96	3	–	–	2 (0.5)	2 (0.5)
75	3	–	–	1 (0.2)	1 (0.2)
130	3	–	–	1 (0.2)	1 (0.2)
182	1	–	–	1 (0.2)	1 (0.2)
ND	1, 2, 3	–	–	20 (4.5)	37 (8.4)
			+	5 (1.1)	
	1, 2, 3	+	–	9 (2.0)	
			+	3 (0.7)	

ND: not determined.

CC30 (440/403, 9.3%), and CC398 (36/440, 8.2%) (Table 1). MRSA strains mainly belonged to CC8 (45/115, 39%), CC5 (18/115, 15.65%), and CC80 (16/115, 14%). Reliable lineage assignment was yielded by the *S. aureus* Genotyping Kit for 90 MRSA strains, which revealed a polyclonal MRSA population. Thus, the most represented MRSA clones were CC8-MRSA-IV, Lyon Clone (24/90), followed by CC80-MRSA-IV PVL$^+$ European CA-MRSA Clone (16/90), the ST8-MRSA-IV PVL$^+$ USA300 (and ACME$^-$ variant) (7/90), and the ST5-MRSA-I Geraldine Clone (5/116). Other MRSA clones, such as Pediatric and New Pediatric, UK-EMRSA-15, CA-MRSA Southwest Pacific Clone, and CA-MRSA Taiwan clone were sporadic (each accounted for less than 4/90 strains). PVL-carrier strains belonged to CC80 (18/105, 17.1%),

Table 2
In vitro activity of ceftobiprole and anti-staphylococcal comparator antibiotics against 440 *S. aureus* strains isolated from respiratory infections in France (2010–2014). *Activité in vitro du céftobiprole et des antibiotiques anti-staphylococciques comparateurs sur les souches de* S. aureus *isolées d'infections broncho-pulmonaires en France, entre 2010 et 2014.*

Bacteria (number of clinical isolates) and antibiotics	MIC (μg/mL)			% of susceptible[a] strains
	MIC_{50}	MIC_{90}	Interval	
All strains ($n = 440$)				
Ceftobiprole	0.5	1	0.12–4	99.8
Ceftaroline fosamil	0.25	0.5	0.12–2	99.8
Vancomycin	1	1	0.5–2	100.0
Daptomycin	0.5	0.5	0.5–1	100.0
Linezolid	2	2	1–8	99.5
Tigecycline	0.25	0.5	0.12–1	98.4
MRSA ($n = 115$)				
Ceftobiprole	1	1	0.5–4	99.1
Ceftaroline fosamil	0.5	1	0.12–2	99.1
Vancomycin	1	1	0.5–2	100.0
Daptomycin	0.5	0.5	0.5–1	100.0
Linezolid	2	2	1–8	98.3
Tigecycline	0.25	0.5	0.12–1	98.3
MSSA ($n = 325$)				
Ceftobiprole	0.5	0.5	0.12–2	100.0
Ceftaroline fosamil	0.25	0.25	0.12–1	100.0
Vancomycin	1	1	0.5–2	100.0
Daptomycin	0.5	0.5	0.5–1	100.0
Linezolid	2	2	1–4	100.0
Tigecycline	0.25	0.5	0.12–1	98.5

[a] The interpretation of results was performed using breakpoints determined by EUCAST.

CC121 (16/105, 15.2%), CC152 (15/105, 14.3%), and CC30 (10/105, 9.5%).

3.2. Ceftobiprole activity against S. aureus

Overall, ceftobiprole was highly active against *S. aureus*, with MICs ranging from 0.12 to 4 mg/L (only one resistant strain, MIC of 4 mg/L). Furthermore, ceftobiprole was twice more active on MSSA strains with MIC_{50} and MIC_{90} of 0.5 mg/L than on MRSA strains with MIC_{50} and MIC_{90} of 1 mg/L (Table 2).

Ceftobiprole displayed equivalent activity on PVL-carrier and non-carrier *S. aureus* strains, with MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L for both groups, although PVL-carrier MSSA strains (MIC_{50} and MIC_{90} of 0.5 mg/L) seemed more susceptible than PVL-carrier MRSA strains (MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L). Moreover, PVL-carrier MRSA strains were slightly more susceptible to ceftobiprole (MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L) than non PVL-carrier MRSA strains (MIC_{50} and MIC_{90} of 1 mg/L).

The genetic background of *S. aureus* strains (agr group and CC) may slightly impact the strain susceptibility to ceftobiprole (Table 3); however, this observation is explained by the large participation of MRSA strains to the agr 1-2-3 and to the CC8 and CC5 groups. Indeed, subpopulations presenting MRSA/MSSA proportions similar to the whole isolate collection had MIC_{50} and MIC_{90} of 0.5 mg/L and of 1 mg/L respectively, while the subpopulation with a majority of MRSA strains (CC8) displayed higher ceftobiprole MIC_{50} and MIC_{90} (1 mg/L), and subpopulation with a high majority (>90%) of MSSA strains (CC15, CC30, and CC398) displayed lower ceftobiprole MIC_{50} and MIC_{90} (0.5 mg/L).

The only ceftobiprole-resistant *S. aureus* strain detected in our selection (MIC = 4 mg/L) was a PVL-non-carrier MRSA strain isolated from tracheal aspirate, presenting with the Glu239Lys mutation in PBP2A, previously associated with low-level resistance in ceftobiprole and ceftaroline fosamil [13]. This strain was resistant to both ceftobiprole and ceftaroline fosamil (MIC = 2 mg/L), but remained susceptible to the other major anti-MRSA agents tested (vancomycin, daptomycin, and linezolid).

3.3. Activity of comparator antibiotics against S. aureus

Ceftaroline fosamil had the same activity profile as ceftobiprole on *S. aureus*, with MICs ranging from 0.12 mg/L to 2 mg/L. The activity was more important on MSSA strains (MIC_{50} and MIC_{90} of 0.25 mg/L) than on MRSA strains (MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L) and a similar activity was observed on PVL-carrier and non-carrier strains with MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L, respectively (Table 2, Fig. 1).

With regard to glycopeptide antibiotics, vancomycin was active against *S. aureus*, with MIC_{50} and MIC_{90} of 1 mg/L for all groups of strains (MSSA, MRSA, PVL-carrier, and PVL-non-carrier). None of the *S. aureus* strains tested was vancomycin-resistant.

Likewise, daptomycin was very active on *S. aureus* with MIC_{50} of 0.5 and 0.25 mg/L, and MIC_{90} of 0.5 mg/L. No resistant strain to daptomycin was observed.

MIC_{50} and MIC_{90} were 2 mg/L for linezolid, the highest MICs of all tested antibiotics. We also observed two linezolid-resistant strains, with MIC of 8 mg/L. These strains were isolated

Table 3
In vitro activity of ceftobiprole and proportion of methicillin-susceptible (MSSA)/methicillin-resistant (MRSA) *S. aureus* strains among the various subpopulations of *S. aureus*, according to agr group and clonal complex (CC).
Activité in vitro du céftobiprole et proportion de souches sensibles (MSSA) et résistantes (MRSA) à la méticilline sur les différentes sous-populations de S. aureus.

Subpopulation (number of strains)	Proportion in the subpopulation		Ceftobiprole MIC	
	MSSA (%)	MRSA (%)	MIC_{50}	MIC_{90}
Agr1 (216)	70.4	29.6	0.5	1
Agr2 (106)	81.1	18.9	0.5	1
Agr3 (91)	67.0	33.0	0.5	1
Agr4 (20)	95.0	5.0	0.5	0.5
CC5 (61)	70.5	29.5	0.5	1
CC8 (69)	34.8	65.2	1	1
CC398 (36)	100.0	0.0	0.5	0.5
CC15 (26)	96.2	3.8	0.5	0.5
CC30 (41)	95.1	4.9	0.25	0.5

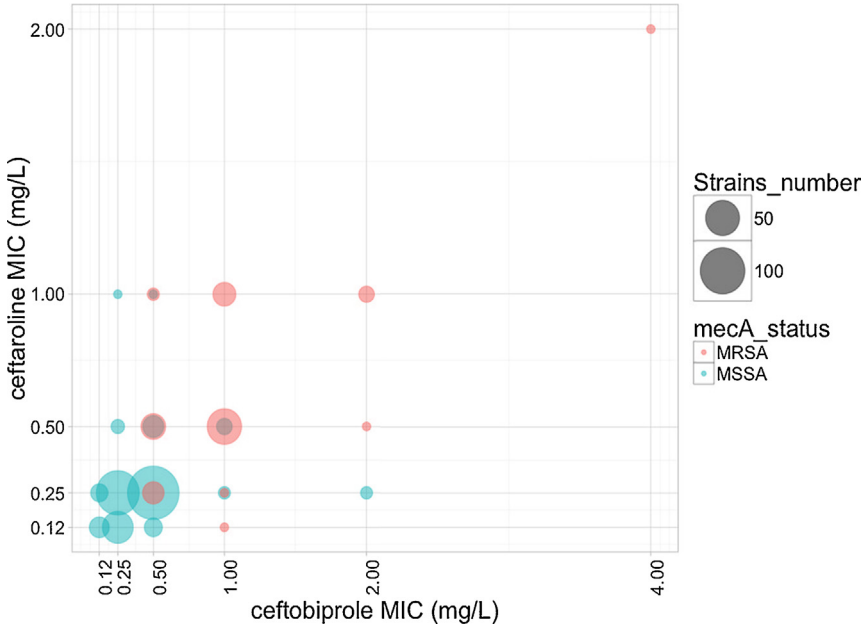

Fig. 1. Correlation between ceftobiprole MICs and ceftaroline fosamil MICs according to the *mecA* status. Circle size varies according to the number of strains tested; blue and red circles represent MSSA and MRSA strains, respectively.
Corrélation entre les CMI de céftobiprole et les CMI de céftaroline en fonction de la présence ou de l'absence du gène mecA. La taille des cercles est proportionnelle au nombre de souches concernées. Les cercles bleus et rouges correspondent respectivement aux souches de S. aureus sensibles à la méticilline (SASM) et résistantes à la méticilline (SARM).

from cystic fibrosis sputum and both remained susceptible to ceftobiprole as well as to the other anti-MRSA agents.

In our study, tigecycline was associated with the most resistant strains (7/440): two MRSA and five MSSA strains; however, altogether MIC_{50} and MIC_{90} were in the same range than other anti-MRSA agents (0.5 and 0.25 mg/L, respectively).

4. Discussion

One of the French Staphylococci National Reference Center missions is to genotype and monitor resistance to antibiotics of isolates responsible for severe clinical presentations, including lower respiratory tract infections. By selecting a representative panel of strains isolated between 2010 and 2014, we determined the in vitro activity of anti-MRSA antibiotic agents. It should be noted that the proportion of MRSA strains tested (26%) is consistent with the MRSA proportion of isolates responsible for severe staphylococcal community-acquired pneumonia recently reported in France (20%) [14]. The genotypic structure of the tested MRSA strains is also consistent with data reported by the European Antimicrobial Resistance Surveillance Network (EARS-Net) [15].

In our study, we observed that ceftobiprole was very active against *S. aureus* isolated from bronchopulmonary infections, regardless of the *mecA* status, with MIC_{90} of 1 mg/L, one of the lowest MIC_{90} reported in studies (ranging from 1 to 4 mg/L) [7–10,16].

Nevertheless, we observed, as previously described, that MSSA strains were more susceptible to ceftobiprole than MRSA strains [9,10,16]. We also observed slightly higher MICs of

ceftobiprole in some subgroups of *S. aureus* studied strains, which was consistent with a higher participation of MRSA strains in those subgroups. These observations suggest a strong link between PBP2a production and higher ceftobiprole MICs. Moreover, we detected one ceftobiprole-resistant strain, which displayed cross-resistance to ceftaroline fosamil and presented D239L amino acid substitution in PBP2a sequence. Considering the major role of PVL in the severity of staphylococcal pneumonia, we analyzed ceftobiprole susceptibility against PVL-positive strains and showed that PVL-carrier *S. aureus* strains were also susceptible to ceftobiprole, including PVL-carrier MRSA strains belonging to the major (European ST80, USA300 ACME±) and minor (CC5 PVL+, ST59 Taiwan, ST30 South West Pacific) CA-MRSA clones spreading in France. Compared with other anti-staphylococcal antibiotics, and especially with other anti-MRSA agents, ceftobiprole displayed MICs slightly higher than ceftaroline fosamil, daptomycin, and tigecycline, but was as effective against *S. aureus* as vancomycin. On the contrary, ceftobiprole was more active than linezolid, with MIC_{90} twice weaker for ceftobiprole than linezolid. Moreover, we detected two resistant strains to linezolid, both isolated from cystic fibrosis sputum and harboring the G2576T mutation in the V domain of the 23S RNA gene (results not shown). These two strains were susceptible to all the other anti-MRSA agents tested, including ceftobiprole.

5. Conclusions

S. aureus resistance is a real healthcare issue, especially during severe infections such as respiratory tract infections. Ceftobiprole could be an effective alternative to vancomycin or linezolid for the management of staphylococcal, including MRSA, HAP, or CAP. Though at present very scarce, close microbiological monitoring of isolates should be maintained to prevent resistant strain diffusion.

Contributors

L.D., C.B., and H.M. performed experiments. M.B., A.T., F.L., F.V., G.L., and O.D. conceived and designed experiments. E.H., G.L., and O.D. analyzed the data and wrote the article.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Liapikou A, Cillóniz C, Torres A. Ceftobiprole for the treatment of pneumonia: a European perspective. Drug Des Devel Ther 2015;9:4565–72, http://dx.doi.org/10.2147/DDDT.S56616.

[2] Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998;339:520–32, http://dx.doi.org/10.1056/NEJM199808203390806.

[3] Leprince C, Desroches M, Emirian A, Coutureau C, Anais L, Fihman V, et al. Distribution and antimicrobial susceptibility of bacteria from adults with community-acquired pneumonia or complicated skin and soft tissue infections in France: the nationwide French PREMIUM study. Diagn Microbiol Infect Dis 2015;83:175–82, http://dx.doi.org/10.1016/j.diagmicrobio.2015.06.007.

[4] Miliani K, Migueres B, Verjat-Trannoy D, Thiolet JM, Vaux S, Astagneau P, et al. National point prevalence survey of healthcare-associated infections and antimicrobial use in French home care settings. May to June 2012. Euro Surveill Bull 2015:20.

[5] Montravers P, Harpan A, Guivarch E. Current and future considerations for the treatment of hospital-acquired pneumonia. Adv Ther 2016, http://dx.doi.org/10.1007/s12325-016-0293-x.

[6] Rouzic N, Janvier F, Libert N, Javouhey E, Lina G, Nizou J-Y, et al. Prompt and successful toxin-targeting treatment of three patients with necrotizing pneumonia due to *Staphylococcus aureus* strains carrying the Panton-Valentine leukocidin genes. J Clin Microbiol 2010;48:1952–5, http://dx.doi.org/10.1128/JCM.01892-09.

[7] Saravolatz LD, Pawlak J, Johnson LB, Saravolatz LD, Husain N. *In vitro* activity of ceftobiprole against meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA) and daptomycin-non-susceptible *S. aureus* (DNSSA). Int J Antimicrob Agents 2010;36:478–80, http://dx.doi.org/10.1016/j.ijantimicag.2010.07.016.

[8] Rossolini GM, Dryden MS, Kozlov RS, Quintana A, Flamm RK, Läuffer JM, et al. Comparative activity of ceftobiprole against Gram-positive and Gram-negative isolates from Europe and the Middle East: the CLASS study. J Antimicrob Chemother 2011;66:151–9, http://dx.doi.org/10.1093/jac/dkq397.

[9] Farrell DJ, Flamm RK, Sader HS, Jones RN. Ceftobiprole activity against over 60,000 clinical bacterial pathogens isolated in Europe, Turkey, and Israel from 2005 to 2010. Antimicrob Agents Chemother 2014;58:3882–8, http://dx.doi.org/10.1128/AAC.02465-14.

[10] Jean S-S, Lee W-S, Yu K-W, Liao C-H, Hsu C-W, Chang F-Y, et al. Rates of susceptibility of carbapenems, ceftobiprole, and colistin against clinically important bacteria collected from intensive care units in 2007: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART). J Microbiol Immunol Infect 2015, http://dx.doi.org/10.1016/j.jmii.2014.12.008.

[11] Banerjee R, Gretes M, Basuino L, Strynadka N, Chambers HF. In vitro selection and characterization of ceftobiprole-resistant methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2008;52:2089–96, http://dx.doi.org/10.1128/AAC.01403-07.

[12] European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, valid from 2016-01-01; 2016 http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf (accessed on May 19, 2016).

[13] Alm RA, McLaughlin RE, Kos VN, Sader HS, Iaconis JP, Lahiri SD. Analysis of *Staphylococcus aureus* clinical isolates with reduced susceptibility to ceftaroline: an epidemiological and structural perspective. J Antimicrob Chemother 2014;69:2065–75, http://dx.doi.org/10.1093/jac/dku114.

[14] Saadatian-Elahi M, Tristan A, Gillet Y, Bes M, Bouchiat C, Dumitrescu O, et al. Community-acquired pneumonia caused by *Staphylococcus aureus* in France: interim results of a prospective cohort study. [Abstract]. In: 24th European Congress of Clinical Microbiology and Infectious Diseases, Barcelonna, Spain. 2014.

[15] Dauwalder O, Lina G, Durand G, Bes M, Meugnier H, Jarlier V, et al. Epidemiology of invasive methicillin-resistant *Staphylococcus aureus* clones collected in France in 2006 and 2007. J Clin Microbiol 2008;46:3454–8, http://dx.doi.org/10.1128/JCM.01050-08.

[16] Pillar CM, Aranza MK, Shah D, Sahm DF. In vitro activity profile of ceftobiprole, an anti-MRSA cephalosporin, against recent Gram-positive and Gram-negative isolates of European origin. J Antimicrob Chemother 2008;61:595–602, http://dx.doi.org/10.1093/jac/dkm492.

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Original article

Prevalence of *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* IgM and IgG antibodies in Tunisian patients presenting with exacerbation of chronic obstructive pulmonary disease

Prévalence des anticorps IgM et IgG dirigés contre Chlamydophila pneumoniae *et* Mycoplasma pneumoniae *chez des patients tunisiens avec exacerbation de bronchopneumopathie chronique obstructive*

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Abstract

Objective. – We aimed to assess the prevalence of *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* acute infections, using serological testing, in patients admitted to the emergency department for acute exacerbations of chronic obstructive pulmonary disease (COPD).

Methods. – We performed a prospective observational study of 100 consecutive patients. Serum specimens were collected at day 0 and day 15. *C. pneumoniae* and *M. pneumoniae* antibodies (IgM and IgG) were tested by commercial ELISA and immunofluorescence assay, respectively.

Results. – We did not observe any acute *M. pneumoniae* infection; however, 11 patients (11%) showed a profile compatible with a recent *C. pneumoniae* infection (nine patients with specific IgM and two with an IgG antibody rise). Demographic and clinical parameters did not differ between patients with and without biological profile of recent *C. pneumoniae* infection.

Conclusion. – *C. pneumoniae* is a pathogen that requires specific antimicrobial treatment. Its detection must always be performed considering its prevalence in patients presenting with acute COPD exacerbations.

Keywords: Chronic obstructive pulmonary disease; *Chlamydophila pneumoniae*; *Mycoplasma pneumoniae*

Résumé

Objectif. – Mesurer la prévalence sérologique des infections récentes à *Chlamydophila pneumoniae* et *Mycoplasma pneumoniae* chez 100 patients consécutifs admis aux urgences pour une exacerbation aiguë de bronchopneumopathie chronique obstructive (BPCO).

Méthodes. – Nous avons réalisé une étude observationnelle prospective. Les anticorps IgM et IgG ont été testés sur des sérums prélevés aux jours 0 et 15, par test Elisa pour *C. pneumoniae* et par immunofluorescence indirecte pour *M. pneumoniae* (trousses commerciales).

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Résultats. – Aucune infection aiguë à *M. pneumoniae* n'a été détectée. En revanche, 11 patients (11 %) avaient un profil sérologique compatible avec une infection récente à *C. pneumoniae* (neuf patients avec IgM spécifiques et deux avec élévation des IgG). Aucune différence significative n'a été notée sur les paramètres cliniques et démographiques testés entre les groupes avec et sans stigmates sérologiques d'infection récente à *C. pneumoniae*.

Conclusion. – *C. pneumoniae* nécessitant un traitement antibiotique adapté, sa recherche systématique paraît justifiée au cours des poussées de BPCO.

Mots clés : Bronchopneumopathie chronique obstructive ; *Chlamydophila pneumoniae* ; *Mycoplasma pneumoniae*

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory process characterized by a progressive airflow limitation and the destruction of parenchyma. Patients affected by this disease experience frequent exacerbations that favor airway inflammation and often lead to hospitalization. COPD exacerbations are characterized by increased sputum volume and purulence, worsening dyspnea and cough [1]. Bacterial and viral infections of the lower respiratory tract account for approximately 80% of all exacerbations [2,3].

Chlamydophila pneumoniae and *Mycoplasma pneumoniae* are common human pathogens causing asymptomatic, mild or severe upper and lower respiratory tract infections. These infections are usually not identified in general health care because the etiology of respiratory tract infections is investigated in only a small proportion of patients, i.e. those who do not respond to conventional antimicrobial therapy or present with severe pneumonia [4]. The role of these pathogens in COPD exacerbations is controversial [5,6]. We aimed to provide recent prevalence data on the distribution of *C. pneumoniae* and *M. pneumoniae* IgG and IgM antibodies in a Tunisian cohort of COPD patients presenting with acute exacerbations, so that an adapted treatment could be established.

2. Patients and methods

We conducted a prospective observational study in the Emergency department of three university hospitals (Monastir, Mahdia, and Sousse) located in the South-East of Tunisia, from May 2013 to March 2015. The Ethics committee in research of Sousse hospital approved the study; a written informed consent was obtained from all patients.

The study population consisted of patients aged over 40 years diagnosed with COPD stages 1–4 as defined by the Global initiative for chronic obstructive lung disease (GOLD), with an acute exacerbation (onset $\leq$ 14 days) [1]. Acute respiratory failure was defined as a worsening of dyspnea associated with at least two of the following characteristics: respiratory rate $\geq$ 24 breaths/min, arterial partial pressure of carbon dioxide $\geq$ 45 mmHg, arterial pH $\leq$ 7.35. A chest radiograph confirming the absence of pneumonia was required. Exclusion criteria were outpatient status, evidence of bronchiectasis, pneumonia, malignancy or severe immunosupression, antimicrobial treatment received in the 10 days preceeding COPD exacerbation, or need for mechanical ventilation. History, physical examination, blood gas, and x-ray results were recorded for all included patients. Except for antibiotics, patients received instrumental and medical therapy according to current guidelines [1]. This study was part of a larger double-blind randomized study aiming at comparing two lines of antibiotic therapy: a two-day treatment with levofloxacin versus a 7-day treatment using the same molecule. Our study is a follow-up of a similar study previously performed in the same setting [7].

Baseline sputum specimens were systematically collected. Semi-quantitative bacterial cultures were performed at the Microbiology laboratory of the university hospital of Monastir as recommended [8]. Results were considered significant if a bacterium of interest was isolated with a count of at least 10^7 CFU/mL. Except for one patient, no sputum specimen was kept frozen for retrospective testing of atypical pathogens by molecular assays.

Four milliliters of blood specimen were systematically collected at enrollment and 15 days later. Included patients who missed the second serological testing were secondarily excluded from the study. The serological tests were carried out in the Microbiology laboratory of the university hospital of Monastir. Serum IgG and IgM antibodies against *M. pneumoniae* were measured using a commercial indirect immunofluorescence assay (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany) as per the manufacturer's instructions. The sensitivity and specificity of the IgG assay were 80% and 100%, respectively, according to the standard values of the kit. The qualitative detection of *C. pneumoniae* IgG and IgM antibodies was performed with a commercial ELISA technique (NovaTec, Immundiagnostica GmbH, Dietzenbach, Germany), as recommended. The sensitivity and specificity of the IgG assay were 90.2% and 91.7%, respectively, according to the standard values of the kit. On the basis of serology standards [9], recent infections with one of those bacteria were defined by the presence of IgM and IgG antibodies in the baseline specimen or if a seroconversion (from negative to positive) occurred between days 0 and 15. Serum specimens exhibiting IgM at day 0 without IgG at day 15 were considered false positive results.

Comparisons of qualitative variables were performed using Chi^2 test and comparisons of means using Mann-Whitney non-parametric test for independent samples (SPSS version 18.1). A P-value < 0.05 was considered significant.

3. Results

A total of 147 consecutive patients presenting with COPD exacerbations were included in the study from May 2013 to March 2015. Forty-seven patients were secondarily excluded because the second serology was not available, which resulted in the final inclusion of 100 patients who were sampled with a first and a second serum specimens.

At enrollment, IgM antibodies to *M. pneumoniae* were negative in all patients. The specific IgG level was positive in 63 patients and negative in 37. No seroconversion was observed (Table 1).

As shown in this table, IgM antibodies to *C. pneumoniae* were detected in both sera of nine patients; eight of them were also found positive for IgG in the first and second serum specimens whereas an IgG rise was observed in the serum of the ninth patient. We observed a seroconversion for IgG antibodies to *C. pneumoniae* without IgM in two more patients, which could correspond to a serological profile of acute reactivation. A serological profile of possible or probable acute infection with *C. pneumoniae* was thus observed in 11% of patients, whereas 59% of them had a serological profile corresponding to a past infection and 30% of them had no antibody against this bacterium (Table 1).

Table 2 depicts the demographic, clinical, laboratory data, duration of levofloxacin treatment, and outcome of the 100 patients according to the absence or presence of serological profile of recent *C. pneumoniae* infection. No difference was observed between the two populations for any of the tested items. The duration of levofloxacin treatment (2 days versus 7 days) was similar between the two groups (Table 2). The recurrence of exacerbations at 6 and 12 months was slightly more frequent and the delay of recurrence was slightly shorter in the *C. pneumoniae* group but sample sizes were too small to reach statistical significance (Table 2). As a consequence, we assessed whether the duration of levofloxacin treatment may have influenced outcome in the subgroup of patients with serological evidence of *C. pneumoniae* infection: three and four recurrence episodes were observed at 6 and 12 months, respectively, in the six patients treated with levofloxacin for 2 days, whereas two recurrence episodes were observed at 6 and 12 months in the five patients treated with that same antibiotic for 7 days; sample sizes are too small to reach statistical significance but this difference tends to indicate that a longer treatment with levofloxacin seems preferable in case of serological profile of *C. pneumoniae* infection.

The conventional cultures of sputum specimens sampled from the 100 patients yielded 16 infections (as defined by a bacterial count of at least 10^7 CFU/mL): *Acinetobacter baumannii* ($n=1$), *Branhamella catarrhalis* ($n=1$), *Escherichia coli* ($n=2$), *Haemophilus influenzae* ($n=1$), *Haemophilus parainfluenzae* ($n=1$), *Klebsiella pneumoniae* ($n=2$), *Pseudomonas aeruginosa* ($n=4$), *Staphylococcus aureus* ($n=1$), *Streptococcus pneumoniae* ($n=2$), and a co-infection with *H. influenzae* and *K. pneumoniae* ($n=1$). With regard to the distribution of conventional bacterial infections based on the presence or absence of serological profile of *C. pneumoniae* acute infection, we observed two infections (*H. influenzae* and *S. pneumoniae*, respectively) in the group of 11 patients characterized as recent *C. pneumoniae* infections (18.2%) as compared with 14 infections in the remaining 89 patients (15.7%) ($P=0.19$ by Chi^2 test).

4. Discussion

Using a large cohort of Tunisian patients presenting with acute COPD exacerbations whose diagnosis was mainly based on commercial serological tests, we observed 11% of possible recent *C. pneumoniae* infections. However, no acute infection was documented for *M. pneumoniae*. The main limitation of our study is the absence of detection of pathogens by nucleic acid testing as this type of assay was, at the time, not available in our laboratory and as most of the respiratory samples were not kept frozen. However, a respiratory specimen from one patient with IgM antibodies to *C. pneumoniae* was retrospectively tested by PCR for *M. pneumoniae* and *C. pneumoniae* and was confirmed positive for *C. pneumoniae* genome (data not shown). Indeed, molecular tests are a good complement to serological testing [5]; they are considered faster, more sensitive, and more specific than culture and serology [10], even if the presence of *C. pneumoniae* DNA without serological profile of an infection can correspond to a persistent asymptomatic carriage of this bacterium [5,11]. The lack of standardized commercial ELISA kits for *C. pneumoniae* is another limitation of our study, with the possible occurrence of nonspecific IgM antibodies, especially when they are detected in the absence of specific IgG together with serological profile of another bacterial infection in the respiratory tract [12,13]. With regard to *C. pneumoniae* IgG, the sensitivity of various immunoassays compared with the microimmunofluorescence assay considered the gold standard ranged from 63 to 95% in the context of respiratory tract infections [5]. Given the high prevalence of IgG antibodies to this bacterium, a high antibody titer on a single sample cannot be considered a criterion of active infection.

C. pneumoniae has been shown to be significantly involved in the occurrence of acute COPD exacerbations, as illustrated by various studies using serological testing. As shown in Table 3 summarizing a total of 503 patients presenting with acute COPD exacerbations (including the present study), the rate of positive cases for *C. pneumoniae* ranged from 4 to 34% with an overall mean of 13.1%, which is very close to the 11% rate observed in our study. Of interest, we show that no difference was observed between the groups of patients presenting with and without evidence of serological acute *C. pneumoniae* infection in terms of demographics, clinical presentation, clinical outcome, or detection of other bacterial agents at a significant level in the respiratory tract. However, these results stress the need for a systematic investigation of serological profile of *C. pneumoniae* recent infection in patients presenting with acute COPD exacerbations as this pathogen would require an antimicrobial treatment based on compounds active on intracellular agents that are not recommended in the first-line treatment of COPD exacerbations [1]. Despite our small sample size,we observed

Table 1
Mycoplasma pneumoniae and *Chlamydophila pneumoniae* serological profiles on two consecutive serum specimens sampled from 100 patients presenting with acute COPD exacerbations.
Profils sérologiques sur deux sérums consécutifs vis à vis de Mycoplasma pneumoniae *et* Chlamydophila pneumoniae *dans une cohorte de 100 patients présentant une poussée aiguë de BPCO.*

1st serum specimen (day 0)		2nd serum specimen (day 15)		Conclusion	*M. pneumoniae* (number of patients)	*C. pneumoniae* (number of patients)
IgM	IgG	IgM	IgG			
−	−	−	−	No infection	37	30
−	+	−	+	Past infection	63	59
+	+	+	+	Acute infection	0	8
+	−	+	+	Acute infection	0	1
−	−	−	+	Reactivation	0	2

(−): no detection of antibodies at the threshold given by the manufacturers of the respective tests.

Table 2
Comparison of various variables in 100 patients hospitalized for COPD exacerbation with and without serological profile of acute *Chlamydophila pneumoniae* infection.
Comparaison de différentes variables chez 100 patients hospitalisés pour une exacerbation de BPCO avec et sans stigmates sérologiques d'infection aiguë à Chlamydophila pneumoniae.

List of tested variables	Serological profile of acute *C. pneumoniae* infection		*P*-value
	No $n = 89$	Yes $n = 11$	
Demographics			
Mean age (years)	67 ± 10.3	63.1 ± 9.7	NS
Percentage of male patients	92.1	90.9	NS
Smoking habits (pack-year)	68.6 ± 152	52 ± 46	NS
Clinical findings at enrollment			
Percentage of stage 4 dyspnea	46.1	27.3	NS
Body Mass Index (kg/m^2)	$27.\ 2 \pm 5.5$	28.3 ± 4.2	NS
Body temperature (°C)	37.4 ± 0.7	37.0 ± 0.5	NS
Respiratory rate (beats per minute)	27.3 ± 11	27.5 ± 3.6	NS
Heart rate (beats per minute)	109.7 ± 25.6	116.4 ± 14.7	NS
Laboratory findings at enrollment			
PaO_2 (kPa)	9.5 ± 3.7	10.0 ± 4.6	NS
$PaCO_2$ (kPa)	6 ± 2	5.5 ± 1.7	NS
pH	7.4 ± 0.1	7.4 ± 0.2	NS
Percentage of oxygen saturation (SaO_2)	89.6 ± 11.1	91.8 ± 7.5	NS
White blood cell count (c/mm^3 × 10^3)	12.5 ± 4.4	15.5 ± 7.9	NS
Hemoglobin (g/dL)	14.3 ± 6.2	14 ± 1.6	NS
Platelet count (× 10^3/μL)	240.0 ± 83.2	245.0 ± 75.5	NS
C-reactive protein (mg/dL)	66.3 ± 67.2	93.5 ± 94.5	NS
Duration of levofloxacin treatment			NS
2 days: number (%)	43 (48.3)	6 (54.5)	
7 days: number (%)	46 (51.2)	5 (45.5)	
Outcome			
Percentage of survivors	91.0	100	NS
Number (%) of exacerbation recurrences			
At 6 months	26 (29.2)	5 (45.4)	NS
At 12 months	32 (35.9)	6 (54.5)	NS
FTI			
At 6 months	118.3 ± 63.1	97.0 ± 49.4	NS
At 12 months	169.6 ± 93.8	114.0 ± 60.7	NS

PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; FTI: free time interval between two acute COPD exacerbations; NS: non-significant by Mann-Whitney test for quantitative variables and by Chi^2 test for qualitative variables between the two groups at a *P*-value of 0.05. Except for percentages and values expressed as units of time (days or months), data is presented as mean ± standard deviation.

an increasing trend of recurrences in patients presenting with serological evidence of *C. pneumoniae* infection when they receive a short quinolone monotherapy (2 days), which is a further reason to look for possible infection with this bacterium at enrollment.

By contrast to *C. pneumoniae*, we did not observe any recent infection with *M. pneumoniae*. As outbreaks of *M. pneumoniae* infection are known to occur approximately every 3 years, our study period is too short for concluding that this bacterium does not play any role in the occurrence of acute COPD

Table 3
Prevalence of serological profiles of acute *Chlamydophila pneumoniae* infection during acute COPD exacerbations in selected studies.
Prévalence de stigmates sérologiques d'infection aiguë à Chlamydophila pneumoniae *au cours d'épisodes aigus de BPCO à partir d'une sélection d'études de la littérature.*

Reference	Study period	Country	Serological assay	Total number of COPD patients	Number (%) of patients presenting with acute *C. pneumoniae* infection
[14]	1999	Turkey	MIF	49	11 (22.4)
[15]	1999–2002	Turkey	MIF	75	13 (17.3)
[16]	1996	Finland	ELISA	29	2 (6.9)
[17]	2001	Turkey	MIF	38	13 (34.2)
[18]	2004	Italy	MIF	45	5 (11.1)
[11]	2005–2008	Greece	MIF	92	4 (4.3)[a]
[19]	2007	Greece	MIF & ELISA	75	7 (9.3)
Present study	2013–2015	Tunisia	ELISA	100	11 (11.0)
			Total	503	66 (13.1)

MIF: microimmunofluorescence assay; ELISA: enzyme-linked immunosorbent assay.
[a] Two of these four serological results were also positive by *C. pneumoniae* PCR assay.

exacerbations. However, this pathogen is more rarely associated with COPD exacerbations than *C. pneumoniae*, although previous studies showed that it was involved in a small proportion of them [6,11,14,15,18].

5. Conclusion

Our study of 100 consecutive Tunisian patients presenting with COPD exacerbation shows an overall prevalence of *C. pneumoniae* acute infection of 11%. This figure is supported by other international study results; it therefore seems reasonable to recommend the diagnosis of this infection in this particular context, with the aim of implementing an adequate antimicrobial treatment. However, the tools used for this diagnosis, based either on serology or on molecular testing, need to be standardized to better define the specific role of *C. pneumoniae* in the pathophysiology of acute COPD exacerbations.

Contribution of authors

S.M., I.T. and M.H.G. performed the serological experiments.
S.M. and S.N. included the patients into the study and analyzed the clinical files.
S.M., B.P. and M.M. analyzed the biological results and wrote the article.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Global initiative for chronic obstructive lung disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016), http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/ (accessed on May 2, 2016).
[2] Brunton S, Carmichael BP, Colgan R, Feeney AS, Fendrick AM, Quintiliani R, et al. Acute exacerbation of chronic bronchitis: a primary care consensus guideline. Am J Manag Care 2004;10:689–96.
[3] Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. Chest 2000;117:380S–5S.
[4] Tuuminen T, Varjo S, Ingman H, Weber T, Oksi J, Viljanen M. Prevalence of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* immunoglobulin G and A antibodies in a healthy Finnish population as analyzed by quantitative enzyme immunoassays. Clin Diagn Lab Immunol 2000;7:734–8.
[5] Papaetis GS, Anastasakou E, Orphanidou D. *Chlamydophila pneumoniae* infection and COPD: more evidence for lack of evidence? Eur J Intern Med 2009;20:579–85.
[6] Lieberman D, Lieberman D, Ben-Yaakov M, Shmarkov O, Gelfer Y, Varshavsky R, et al. Serological evidence of *Mycoplasma pneumoniae* infection in acute exacerbation of COPD. Diagn Microbiol Infect Dis 2002;44:1–6.
[7] Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-control trial. Lancet 2001;358:2020–5.
[8] Société française de microbiologie. In: REMIC, Société française de microbiologie, editors. Infections bronchopulmonaires (hors tuberculose et mucoviscidose). 2015. p. 179–92.
[9] Dowell SF, Peeling RW, Boman J, Carlone GM, Fields BS, Guarner J, et al. Standardizing *Chlamydia pneumoniae* assays: recommendations from the Centers for disease control and prevention (USA) and the Laboratory centre for disease control (Canada). Clin Infect Dis 2001;33:492–503.
[10] Ieven M. Currently used nucleic acid amplification tests for the detection of viruses and atypicals in acute respiratory infections. J Clin Virol 2007;40:259–76.
[11] Nakou A, Papaparaskevas J, Diamantea F, Skarmoutsou N, Polychronopoulos V, Tsakris A. A prospective study on bacterial and atypical etiology of acute exacerbation in chronic obstructive pulmonary disease. Future Microbiol 2014;9:1251–60.
[12] Miyashita N, Obase Y, Fukuda M, Shoji H, Mouri K, Yagi S, et al. Evaluation of serological tests detecting *Chlamydophila pneumoniae*-specific immunoglobulin M antibody. Intern Med 2006;45:1127–31.
[13] Miyashita N, Kawai Y, Yamaguchi T, Ouchi K, Kobashi Y, Oka M. Evaluation of false-positive reaction with ELISA for the detection of *Chlamydophila pneumoniae*-specific IgM antibody in adults. Jpn J Infect Dis 2010;63:150–1.
[14] Mogulkoc N, Karakurt S, Isalska B, Bayindir U, Celikel T, Korten V, et al. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. Am J Respir Crit Care Med 1999;160:349–53.

[15] Erkan L, Uzun O, Findik S, Katar D, Sanic A, Atici AG. Role of bacteria in acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2008;3:463–7.
[16] Von Hertzen L, Isoaho R, Leinonen M, Koskinen R, Laippala P, Töyrylä M, et al. *Chlamydia pneumoniae* antibodies in chronic obstructive pulmonary disease. Int J Epidemiol 1996;25:658–64.
[17] Karnak D, Beng-sun S, Beder S, Kayacan O. *Chlamydia pneumoniae* infection and acute exacerbation of chronic obstructive pulmonary disease (COPD). Respir Med 2001;95:811–6.
[18] Meloni F, Paschetto E, Mangiarotti P, Crepaldi M, Morosini M, Bulgheroni A, et al. Acute *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in community-acquired pneumonia and exacerbations of COPD or asthma: therapeutic considerations. J Chemother 2004;16:70–6.
[19] Papaetis GS, Anastasakou E, Tselou T, Karapanagiotou E, Botsis T, Roussou P, et al. Serological diagnosis of *Chlamydophila pneumoniae* infection in Greek COPD patients by micro-immunofluorescence and ELISA. Med Sci Monit 2008;14:MT27–35.

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Cas clinique

Un cas de brucellose atypique

An atypical presentation of human brucellosis

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1. Introduction

La brucellose est une anthropozoonose dont l'incidence est extrêmement variable d'un pays à l'autre. En France, du fait de sa rareté, elle n'est plus un problème majeur de santé publique. Le diagnostic est d'autant plus délicat pour le clinicien. Nous décrivons dans ce cas une forme rare de brucellose avec atteintes neurologiques et cutanées.

2. Présentation du cas

Un patient âgé de 72 ans, d'origine algérienne ayant effectué un voyage au pays six semaines avant, est adressé pour purpura évoluant depuis 15 jours. À l'arrivée le patient est fébrile ; il présente des lésions cutanées de type purpura vasculaire aux membres inférieurs, au niveau de l'abdomen et des membres supérieurs sans autre anomalie clinique. Biologiquement, on observe un syndrome inflammatoire, une anémie inflammatoire et une discrète cytolyse hépatique. L'examen cytobactériologique des urines (ECBU) est stérile, la radiographie thoracique ne montre aucun foyer, l'échographie abdominale est sans particularité. Les 3 flacons d'hémocultures réalisés reviennent positifs à *Brucella melitensis*. Un traitement par rifampicine (900 mg IV) et doxycycline (100 mg × 2/j per os) est alors débuté. Devant la persistance de l'hyperthermie, le patient recevra 2 injections de gentamicine (300 mg).

En reprenant l'interrogatoire, le patient reconnaît consommer régulièrement du lait cru de brebis en Algérie.

Le bilan de cette brucellose n'a pas montré d'atteinte ostéoarticulaire à la scintigraphie osseuse et au TEP-scanner et pas d'endocardite à l'échographie transoesophagienne. La biopsie cutanée montrait des remaniements inflammatoires polymorphes dermo-épidermiques à tropisme périvasculaire sans aspect caractéristique d'une vascularite.

Le patient est devenu apyrétique au 7e jour avec, par contre, une majoration du syndrome inflammatoire et l'apparition d'une orchi-épididymite droite, sans abcès objectivé à l'échographie.

Au 9e jour de traitement, le patient a présenté des épisodes d'aphasie de 20 minutes récidivants, sans autre anomalie neurologique, toujours apyrétique. L'IRM cérébrale injectée ne montrait pas d'anomalie, la ponction lombaire (PL) retrouvait 25 leucocytes (les autres analyses ne pouvant être réalisées dans le laboratoire NSB3 de l'hôpital). L'électroencéphalogramme (EEG) révélait des crises partielles complexes focalisées en central gauche. Le patient était mis sous clobazam et de la ceftriaxone (2 g) était ajoutée pour le traitement de la neurobrucellose probable. Malgré cela, au bout de 24 h, le patient était transféré en réanimation pour état de mal épileptique. Après mise sous lacosamide et fortes doses de clobazam, son état neurologique s'est amélioré sans nouvelle récidive de crise partielle. Les anal-

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yses du liquide céphalorachidien (LCR) n'objectiveront pas la présence de *Brucella* que ce soit en culture, par PCR ou par sérologies.

Le traitement par ceftriaxone-doxycycline-rifampicine a été poursuivi 1 mois, puis un relais par co-trimoxazole (800 mg/160 mg × 2 per os)-doxycycline-rifampicine a été instauré pour 5 mois supplémentaires. Après 6 mois de traitement, le patient est totalement asymptomatique. Sur le plan neurologique, l'EEG de contrôle est normal, le clobazam a été sevré et le lacosamide a été arrêté à 1 an avec une évolution toujours favorable.

3. Discussion

La brucellose est l'anthropozoonose la plus répandue dans le monde ; elle serait responsable de 500 000 nouveaux cas humains par an [1]. Son incidence et sa prévalence varient largement entre les pays dits développés où la maladie est devenue rare et ceux qui, en l'absence de programmes de lutte nationaux, recensent de nombreux cas humains et animaux. En France, les programmes de lutte datent de la fin des années 1960. En 2015, 19 cas ont été déclarés et validés et sont très majoritairement importés [1].

La contamination humaine se fait le plus souvent soit par l'ingestion d'aliments contaminés, soit par aérosolisation de la bactérie ou contact direct. Les principaux aliments responsables de brucelloses humaines sont les produits à base de lait cru. En France, l'espèce la plus fréquente est *B. melitensis* biovar 3. Tous les cas de brucellose confirmés au Centre national de référence sont soit des cas importés, soit des contaminations de personnel de laboratoire. Les zones présumées de contamination sont principalement la Turquie, le Maghreb et le Moyen-Orient. Notre patient présentait un mode de contamination classique, pour un cas importé ayant consommé un produit laitier cru en zone enzootique (Algérie).

L'infection brucellienne se déroule typiquement en 3 phases, chacune d'elle pouvant rester paucisymptomatique voire muette. L'incubation varie entre quelques jours et plusieurs semaines mais des durées plus longues ont été décrites (jusqu'à 5 mois). L'infection aiguë est décrite classiquement avec une fièvre ondulante sudoro-algique, qui ne serait pas si fréquente en pratique. Il s'y associe une sensation de malaise avec frissons, courbatures, arthromyalgies, céphalées. L'examen retrouve parfois des adénopathies, une hépatosplénomégalie.

La brucellose subaiguë peut succéder à une période aiguë bruyante ou être révélatrice de l'infection et durer quelques mois. Elle est marquée par des focalisations essentiellement ostéoarticulaires mais également hépatiques, spléniques, génitales, cardiaques et neurologiques.

La brucellose chronique regroupe, d'une part, des rechutes ou réactivations (foyers secondaires osseux) rencontrées dans 10 % des cas, d'autre part, des formes dites psycho-neurologiques caractérisées par des symptômes chroniques de type fatigue ou dépression pour lesquelles le niveau de preuve du lien entre brucellose et les symptômes est faible.

Dans notre cas, le patient a présenté une forme aiguë, avec des manifestations inhabituelles. En effet, même si des atteintes cutanées sont décrites, le purpura reste exceptionnel. Les atteintes cutanées liées à *Brucella* seraient présentes dans 5 à 14 % des cas selon les études [2–5]. Ces lésions peuvent être présentes aux 3 stades de la maladie. Berger et al. [2] ont décrit une classification des lésions cutanées rencontrées dans la brucellose. Il y a tout d'abord les lésions liées au contact direct avec l'agent pathogène, rencontrées la plupart du temps chez les professionnels de l'élevage, avec des abcès au point d'inoculation ou des lésions de dermatite. Ensuite, des manifestations cutanées transitoires peuvent être notées : éruption papulaire ou urticarienne, érythème noueux ou ressemblant, érythème malaire, lésions érysipéloïde, psoriasiformes ou impétiginisées, eczéma, œdème, lésions ressemblant au pityriasis rosé. Enfin, des lésions généralisées comprenant des abcès cutanés multiples ou des ulcérations multiples peuvent être observées. Également, des lésions cutanées systémiques ou vasculaires avec purpura et emboles peuvent être rencontrées. Selon les séries [2–5], les lésions les plus fréquentes sont les éruptions maculopapulaires, les lésions ressemblant à l'érythème noueux ou les lésions urticariennes. Ariza et al. [3] ont rapporté deux cas de purpuras extensifs au cours de bactériémies sévères associées à des troubles de l'hémostase. Cela n'est pas le cas de notre patient qui avait un bilan de coagulation normal.

L'atteinte génito-urinaire de la brucellose est plus classique, c'est la seconde localisation focale la plus fréquente après les atteintes ostéoarticulaires, soit 2 à 20 % des brucelloses [6]. L'orchi-épidydimite unilatérale en est la manifestation la plus fréquente La plupart du temps, il n'y a pas d'anomalie du sédiment urinaire. L'évolution est en général favorable sous antibiotique seul. Les complications potentielles sont l'abcédation, la fistulisation, voire la nécrose devant conduire à l'orchidectomie pour les formes vues tardivement.

Enfin, la neurobrucellose peut se développer à n'importe quel stade de la maladie, représentant 1 à 7 % des brucelloses. Les présentations sont très variables et comprennent des polyradiculonévrites, des atteintes des nerfs crâniens, des méningites ou méningo-encéphalites, des myélites, des abcès, des formes psychiatriques, des vascularites et quelques cas d'épilepsie. Les critères diagnostiques sont mal définis, reposant sur des éléments cliniques et des analyses du LCR. Guven et al. [7] a repris une cohorte de 48 patients ayant eu un diagnostic de neurobrucellose (tous stades confondus). Les éléments de la PL orientant étaient une hyperprotéinorachie (58 % des cas), une hypoglycorachie (33 % des cas), une pléiocytose à prédominance lymphocytaire (58 %). B*rucella* était rarement détectée dans le LCR (15 %). Pour un *cut-off* à 1/8, le test d'agglutination dans le LCR, avait une sensibilité de 94 % et une spécificité de 96 %. Par contre, seulement 27 % des patients avaient des lésions évocatrices en imagerie (IRM ou TDM). Yetkin et al. [8] décrivent également les données concernant 20 cas de neurobrucelloses. Seulement 18 patients avaient eu une étude du LCR. La pléiocytose et l'hyperproteinorachie étaient notées dans tous les cas. De même que dans la précédente étude, les résultats d'imagerie étaient normaux pour 14 des 20 patients. Ces données sont intéressantes car à ce jour, peu d'études ont été réalisées sur ces atteintes neurologiques et elles sont difficilement généralis-

ables puisqu'il s'agit d'études rétrospectives sur un petit nombre de cas englobant toute forme neurologique à tout stade confondu.

Dans notre cas, nous avons conclu à une neurobrucellose devant la présence d'une méningite à la PL et la présence de signes neurologiques non expliqués par ailleurs, même si peu d'éléments objectifs (imagerie, tests du LCR) ont pu le confirmer.

Le traitement de la neurobrucellose est non consensuel. Erden et al. [9] ont réalisé une étude rétrospective comparant 3 régimes de traitement : ceftriaxone-doxycycline-rifampicine (P1), bactrim-doxycycline-rifampicine (P2), et P1 suivi de P2 quand la ceftriaxone est arrêtée. Quand on considère globalement les issues négatives (échec et rechutes), les traitements avec la ceftriaxone seraient plus efficaces. La durée du traitement est mal définie, prolongée certainement, comprise entre 4 et 6 mois.

4. Conclusion

La brucellose peut avoir des présentations très variées et trompeuses qui sont d'autant plus difficiles à reconnaître dans les pays où elle n'est plus endémique. Les critères diagnostiques de certaines formes focalisées et leur traitement sont encore mal codifiés et nécessiteraient des études prospectives.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

Contribution des auteurs

A.L. Blanc-Gruyelle, X. Lemaire, A. Guaguere ont participé à la prise en charge du patient.

A. Sotto, E. Senneville et J.P. Lavigne ont aidé à la prise en charge du patient par leurs avis.

A.L. Blanc-Gruyelle a écrit l'article.

X. Lemaire et J.P. Lavigne ont participé à la relecture et la modification de l'article.

Références

[1] Anonyme. Données épidémiologiques 2015, rapport de l'Institut national de veille sanitaire, http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Zoonoses/Brucellose [consulté le 19/04/2016].
[2] Berger TG, Guill MA, Goette DK. Cutaneous lesions in brucellosis. Arch Dermatol 1981;117:40–2.
[3] Ariza J, Servitje O, Pallares R, Fernandez Viladrich P, Rufi G, Peyri J, et al. Characteristic cutaneous lesions in patients with brucellosis. Arch Dermatol 1989;125:380–3.
[4] Metin A, Akdeniz H, Buzgan T, Delice I. Cutaneous findings encountered in brucellosis and review of the literature. Int J Dermatol 2001;40:434–8.
[5] Akcali C, Savas L, Baba M, Turunc T. Seckin. Cutaneous manifestations in brucellosis: a prospective study. Adv Ther 2007;24:706–11.
[6] Navarro-Martinez A, Solera J, Correidora J, Beato JL, Martinez-Alfaro E, Atienzar M, et al. Epididymoorchitis due to B*rucella mellitensis:* a retrospective study of 59 patients. Clin Infect Dis 2001;33:2017–22.
[7] Guven T, Ugurlu K, Ergonul O, Celikbas AK, Gok SE, Comoglu S, et al. Neurobrucellosis: clinical and diagnostic features. Clin Infect Dis 2013;56:1407–12.
[8] Yetkin MA, Bulut C, Erdinc FS, Oral B, Tulek N. Evaluation of the clinical presentations in neurobrucellosis. Int J Infect Dis 2006;10:446–52.
[9] Erdem H, Ulu-Kilic H, Kilic S, Karahocagil M, Shehata G, Eren-Tulek N. Efficacy and tolerability of antibiotic combinations in neurobrucellosis: results of the Istanbul study. Antimicrob Agents Chemother 2012;56:1523–8.

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Cas clinique

Cystite incrustante à *Corynebacterium urealyticum*

Encrusted cystitis by Corynebacterium urealyticum

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Mots clés : *Corynebacterium urealyticum* ; Cystite incrustante ; Struvite ; Calcifications vésicales

Keywords: *Corynebacterium urealyticum*; Encrusted cystitis; Struvite crystals; Bladder calcifications

1. Introduction

Corynebacterium urealyticum est un bacille à gram positif, impliqué dans la cystite incrustante, décrite pour la première fois en 1914 par J. François [1]. Cette entité est mal connue, notamment des infectiologues, et la pathogénicité de *C. urealyticum* est souvent remise en question, considérée comme une contamination.s

C. urealyticum est une bactérie à activité uréasique forte [2]. L'uréase scinde la molécule d'urée présente dans les urines en ammoniac et carbonate, ce qui alcalinise les urines et entraîne la présence de cristaux (struvite), par la précipitation de phosphates ammoniaco-magnésiens. Les dépôts de struvite sur la muqueuse vésicale sont responsables de la cystite incrustante, qui se manifestent en général par une dysurie, des douleurs susspubiennes, une hématurie, l'élimination de calculs de struvite dans les urines, des urines troubles.

2. Présentation des cas

Nous décrivons les cas de quatre patients pris en charge au centre hospitalier de Rodez pour une cystite incrustante.

2.1. Patient 1

Un patient de 83 ans présentait comme antécédent un cancer de prostate traité par prostatectomie et radiothérapie en 1993, compliqué d'urétrite radique, avec cystostomie chirurgicale réalisée en 2012. À partir de 2014, il consultait fréquemment pour des problèmes avec sa sonde de cystostomie (le ballonnet se perçait ou la sonde se bouchait), avec apparition d'une uretérohydronéphrose bilatérale, uretères dilatés jusqu'au méat vésical et aspect calcifié de leur portion distale. À posteriori, dès mai 2014, plusieurs ECBU mettaient en évidence un *C. urealyticum*, avec présence de cristaux de phosphates ammoniaco-magnésiens. En 2015, le scanner retrouvait une vessie de petite taille, avec calcifications circonférentielles pariétales d'aspect feuilleté. Devant un tableau de cystite incrustante compliquée, il a bénéficié d'une cystectomie fin 2015, avec uretérostomie, suivie d'un traitement par teicoplanine pendant 6 semaines. L'examen anatomopathologique retrouvait une fibrose importante avec ulcérations, calcifications, lésions granulomateuses et en profondeur des infiltrats inflammatoires (Fig. 1). Le traitement antibiotique a été bien toléré. Les ECBU de contrôle ne retrouvaient pas de *C. urealyticum*.

2.2. Patient 2

Un patient de 86 ans, aux antécédents de résection transurétrale de prostate, en rétention chronique d'urine, a bénéficié

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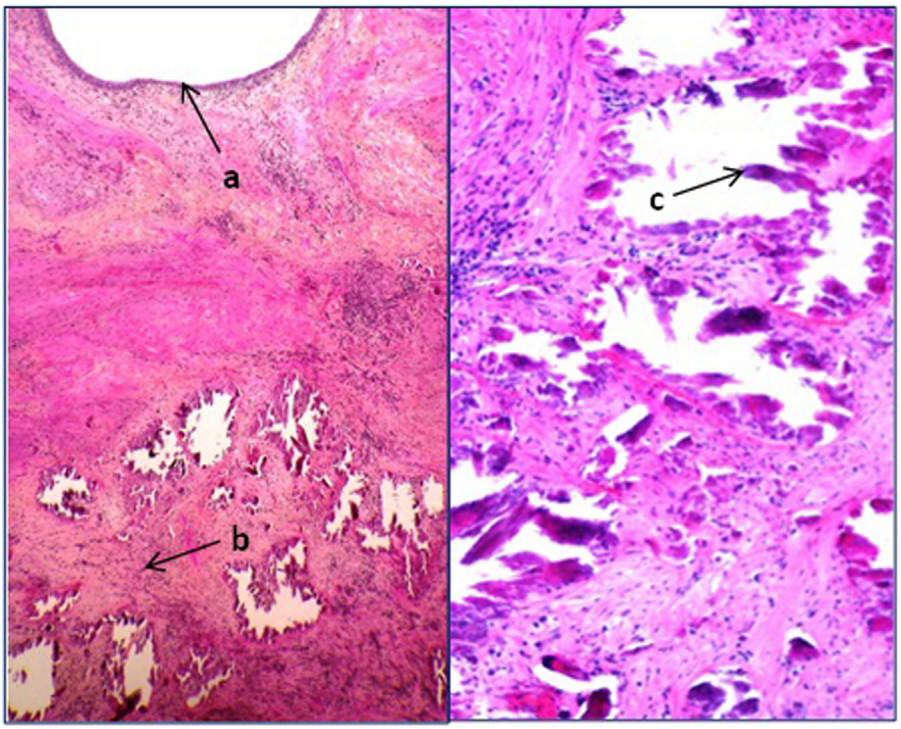

Fig. 1. Examen anatomopathologique patient 1. a : revêtement urothélial superficiel ; b : infiltrat ; inflammatoire ; c : calcification au sein d'un tissu inflammatoire. *Pathological examination patient 1.*

d'un cathéter sus-pubien, en raison d'une pose de sonde urinaire difficile. L'ECBU retrouvait un *C. urealyticum*, avec présence d'assez nombreux cristaux de phosphates ammoniaco-magnésiens. À moins d'un mois, une cystoscopie a retrouvé une sténose serrée du col de la vessie (levée par voie endoscopique), avec un aspect de cystite incrustante dans la région cervicale, réséquée en partie. L'examen anatomopathologique retrouvait des ulcérations et des remaniements inflammatoires et nécrotiques pariétaux. Le scanner, réalisé après la résection endoscopique, ne retrouvait pas de calcifications, mais une paroi vésicale épaissie. Le patient a été traité par teicoplanine, pendant 4 semaines après la résection endoscopique, bien toléré, sans signe de rechute sous traitement. Le patient a été perdu de vue et n'a pas bénéficié de réévaluation à l'arrêt du traitement.

2.3. Patient 3

Une patiente de 77 ans, sans antécédent urologique, a été hospitalisée pour un AVC, avec mise en place d'une sonde vésicale, retirée 21 jours plus tard. Elle a présenté quelques jours plus tard une hématurie, avec apparition d'un syndrome fébrile et identification sur l'ECBU d'un *C. urealyticum*. La cristallurie était négative. Une cystoscopie a été réalisée, retrouvant des plaques calcifiées. Aucun geste n'a été réalisé au vu de son état général. Le scanner a confirmé la présence d'importantes calcifications pariétales vésicales, de siège postéro-supérieur et au niveau de la corne vésicale droite. La patiente a bénéficié d'un traitement par teicoplanine, poursuivi 6 semaines après l'endoscopie. Le scanner de contrôle réalisé plus d'un mois après l'arrêt des antibiotiques retrouvait une disparition des calcifications (Fig. 2). Les ECBU de contrôle ne retrouvaient pas de *C. urealyticum*.

2.4. Patient 4

Un patient de 74 ans, aux antécédents de carcinomes urothéliaux, avec prise en charge par résection endoscopique et BCGthérapie, a développé quelques années plus tard une hydronéphrose, avec sur le scanner une paroi vésicale épaissie et présence de zones calcifiées. L'endoscopie a retrouvé une paroi vésicale complètement nécrosée, avec calcifications intravésicales. Il a bénéficié d'une résection endoscopique des zones nécrosées avec pose de 2 sondes urétérales. L'anatomopathologie a retrouvé de la nécrose et des granulomes épithélioïdes, bordés par une bande lymphocytaire. Il a été traité par teicoplanine pendant 2 semaines, avec acidification des urines par soda (pH urinaire contrôlé à 6,5). L'endoscopie de contrôle réalisée à distance des antibiotiques ne retrouvait pas de récidive de cystite incrustante, mais une diminution des capacités de la vessie. Par la suite, le patient a présenté plusieurs candiduries.

3. Discussion

Le diagnostic de cystite incrustante à *C. urealyticum* est souvent méconnu ou posé avec retard, comme pour notre patient 1.

C. urealyticum est une bactérie d'identification difficile [3], qui pousse lentement sur milieu spécifique (incubation sur

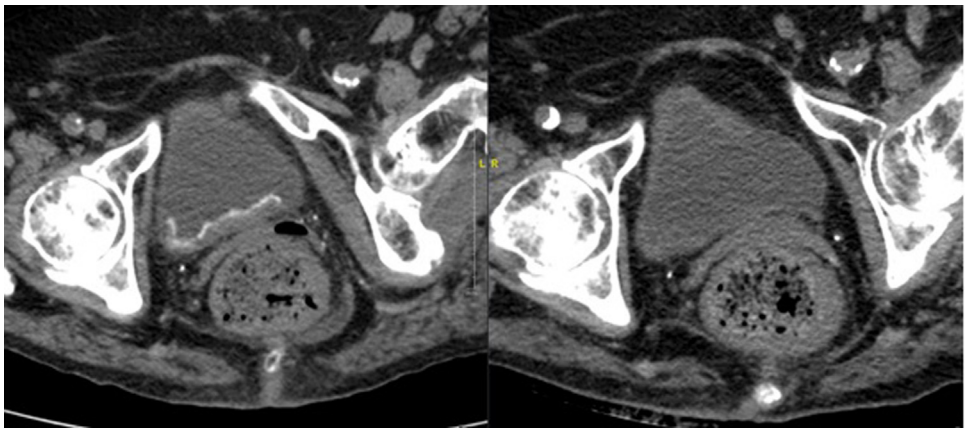

Fig. 2. Scanner patient 3. À gauche : scanner avant traitement : calcifications paroi postérieure de la vessie ; à droite : scanner après 6 semaines de telcoplanine : disparition des calcifications.
Computed tomography scan patient 3.

gélose au sang à 37 °C). En cas de suspicion de cystite incrustante, il faut prévenir le laboratoire pour faire cette recherche, qui devrait également être réalisée en cas d'urines alcalines avec présence de cristaux de struvite.

Tous nos patients présentaient au moins un facteur de risque de cystite incrustante [4], qui sont une pathologie urologique sous-jacente (principalement de la vessie), le port prolongé de sonde urinaire, les antécédents d'infection urinaire, les anomalies de la vessie par traumatisme, tumeur ou administration intravésicale de traitement cytotoxique. En présence d'un facteur de risque, il ne faut pas considérer *C. urealyticum* comme un contaminant, et rechercher une cystite incrustante.

Plusieurs examens aident à porter le diagnostic [2]. L'identification de *C. urealyticum* dans l'ECBU, avec présence de cristaux de struvite (phosphates ammoniaco-magnésiens), présents chez la moitié de nos patients, est en général l'élément initial faisant évoquer cette pathologie. Le pH alcalin des urines, secondaire à l'activité uréasique de *C. urealyticum*, est généralement associé. L'échographie et le scanner sont les examens clés [5] : ils retrouvent des plaques calcifiées des parois de la vessie, avec un œdème important, et recherchent une urétéro-hydronéphrose associée. La cystoscopie permet de confirmer le diagnostic avec des plaques calcifiées et des zones ulcérées, surtout au niveau du trigone, de la paroi postérieure ou du col de la vessie. L'examen anatomopathologique retrouve au niveau superficiel un tissu nécrotique ulcéré contenant des calcifications, puis une couche inflammatoire riche en colonies bactériennes, lymphocytes et polynucléaires [6]. L'ensemble de ces examens chez un patient présentant des facteurs de risque permet de confirmer le diagnostic. Chez notre patient 4, l'ECBU n'a pas retrouvé *C. urealyticum*, mais le terrain, le scanner et l'endoscopie étant en faveur, le diagnostic a été retenu, avec un traitement efficace.

Le traitement classique comporte 3 parties : le traitement antibiotique, l'élimination des plaques par résection endoscopique et l'acidification des urines [6].

Du fait des résistances naturelles (résistance aux bétalactamines, sensibilité conservée aux glycopeptides) [7], le traitement antibiotique généralement proposé est la teicoplanine pendant 4 à 6 semaines, utilisée chez tous nos patients. Ce glycopeptide nécessite des perfusions quotidiennes et un dosage résiduel pour adapter les doses. L'antibiothérapie est une partie du traitement. Mais, notamment en cas d'état général altéré, le traitement antibiotique seul peut être envisagé, à privilégier si le diagnostic est précoce, avec une antibiothérapie prolongée (en général 6 semaines), comme pour notre patient 3.

La résection endoscopique est une autre partie du traitement, mais n'est parfois pas réalisable du fait du terrain. Elle a permis un succès thérapeutique, en association au traitement antibiotique, chez les patients 2 et 4, alors même que le diagnostic était tardif chez le patient 4, qui présentait ces calcifications depuis plusieurs mois à années. Elle est à renouveler si besoin. Elle est d'autant plus importante que les calcifications sont étendues.

L'acidification des urines est recommandée, mais difficile à mettre en place (pas de solution acide disponible sur notre hôpital). Le patient 4 a bu beaucoup de soda, ce qui a permis d'acidifier les urines (pH urinaire contrôlé). Il est classiquement proposé d'acidifier les urines par irrigation directe continue par solution de Thomas [8]. Les complications de l'acidification sont la douleur locale, l'acidose métabolique et la candidurie (cas de notre patient 4). Nos 3 autres patients ont évolué favorablement, sans acidification.

La cystite incrustante, qui se complique très rarement de façon aiguë, provoque surtout des complications à long terme, et une gêne importante chez les patients. Elle peut entraîner une diminution des capacités de la vessie (cas de notre patient 4), une dégradation de la fonction rénale liée à l'hydronéphrose, et des complications liées au traitement : complications liées à la teicoplanine, liées à l'acidification des urines, et selon l'évolution nécessité parfois de chirurgie, type cystectomie (cas de notre patient 1).

4. Conclusion

La cystite incrustante à *C. urealyticum* est une pathologie qui doit être connue des cliniciens, notamment des infectiologues. Le pronostic fonctionnel est amélioré par un diagnostic précoce. *C. urealyticum* ne doit pas être considéré comme une

contamination en cas de pathologie urologique sous-jacente ou en cas de présence de cristaux de struvite dans des urines alcalines.

Le traitement antibiotique seul peut se discuter ; il peut à lui seul faire disparaître les calcifications. La résection endoscopique est d'autant plus importante que les calcifications sont étendues. L'acidification des urines est difficile à réaliser en pratique.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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P. Lansalot-Matras : prise en charge des patients, rédaction du manuscrit, R. Bosc : analyse anatomopathologique, B. Dubourdieu : analyse bactériologique, G. Crenn : prise en charge des patients, N. Berthod : prise en charge des patients, M. Loriette : prise en charge des patients, relecture du manuscrit, B. Marchou : encadrement.

Références

[1] Francois J. La cystite incrustée. J Urol Medicale Chir 1914;5:35–52.
[2] Soriano F, Tauch A. Microbiological and clinical features of *Corynebacterium urealyticum*: urinary tract stones and genomics as the Rosetta Stone. Clin Microbiol Infect 2008;14:632–43.
[3] Riegel P. Les corynébactéries, aspects bactériologiques et cliniques. Ann Biol Clin (Paris) 1998;56:285–96.
[4] Soriano F, Aguado JM, Ponte C, Fernández-Roblas R, Rodríguez-Tudela JL. Urinary tract infection caused by *Corynebacterium* group D2: report of 82 cases and review. Rev Infect Dis 1990;12:1019–34.
[5] Thoumas D, Darmallaicq C, Pfister C, Savoye-Collet C, Sibert L, Grise P, et al. Imaging characteristics of alkaline-encrusted cystitis and pyelitis. AJR Am J Roentgenol 2002;178:389–92.
[6] Meria P, Desgrippes A, Arfi C, Le Duc A. Encrusted cystitis and pyelitis. J Urol 1998;160:3–9.
[7] Riegel P. Actualités de l'épidémiologie et du role pathogène des corynébactéries. Antibiotiques 2006;8:153–61.
[8] Hertig A, Duvic C, Chretien Y, Jungers P, Grünfeld JP, Rieu P. Encrusted pyelitis of native kidneys. J Am Soc Nephrol 2000;1:1138–40.

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Case report

Seven hypervirulent ST380 *Klebsiella pneumoniae* septic localizations

Sept localisations septiques de Klebsiella pneumoniae *hypervirulente ST380*

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Mots clés : *Klebsiella pneumoniae* ; Métastase septique

1. Introduction

Klebsiella pneumoniae (Kp) is a frequent pathogen that may harbor virulence factors and cause disseminated infections even in immunocompetent hosts. We report a case of disseminated Kp infection with seven septic localizations and briefly review the literature on hypervirulent Kp (hvKp).

2. Case presentation

A 56-year-old immunocompetent Caucasian man without any medical history, apart from tobacco use and a weaned chronic alcoholism, presented with febrile coma (Glasgow Coma Scale 7) associated with recent chest pain, dyspnea, and cough. Initial physical examination found neck stiffness, bilateral pulmonary crackles, abolition of bilateral breath sounds in pulmonary bases, and left knee arthritis. The patient had not received any non-steroidal anti-inflammatory drugs. Initial biology showed marked inflammatory syndrome with elevated leucocyte count (24,000/mm^3, neutrophils 91%), fibrinogen (>12 g/l), C-reactive protein (474 mg/l), and procalcitonin (4.47 ng/ml). Creatinine serum level was 66 μmol/l. HIV serology was negative. The remainder of the initial biology was unremarkable. The initial non-contrast computed tomography scan revealed the presence of cerebral edema, a right pleural effusion of moderate abundance, an 8-mm pericardial effusion, mediastinal adenopathies, and an alveolar syndrome in the right upper lobe with air bronchogram and a necrotic aspect. We also observed bilateral pseudo-nodular pulmonary infiltrates and diffuse ground glass opacities consistent with an acute respiratory distress syndrome. The bacteriological screening found the same pattern of *K. pneumoniae* with no acquired resistance in a purulent CSF with low glucose levels and high levels of proteins, the pericardium (after pericardotomy for an acute purulent tamponade), the lung (Fig. 1) (in a necrotizing pneumonia), the blood cultures (one positive blood culture on the first day of hospitalization), and urine sample. Brain MRI (Fig. 2) found many bilateral diffuse cerebral abscesses. Transthoracic and transesophageal echocardiography found no endocarditis. Left knee septic arthritis was also suspected with a minor effusion that could not be drained. Initial management consisted in antibiotic therapy with cefotaxime (300 mg/kg/d) and gentamicin (8 mg/kg/d) at high doses for meningitis, mechanical ventilation, renal replacement therapy for oligoanuric acute renal failure, and catecholamine use. Multiplex PCR was performed to determine capsular serotype K1 or K2 and the presence of the main virulence factors [1]. The capsular serotype was K2. PCR revealed the presence of the *rmp*A gene, which is a plasmid-mediated regulator of extracellular polysaccharide synthesis and the

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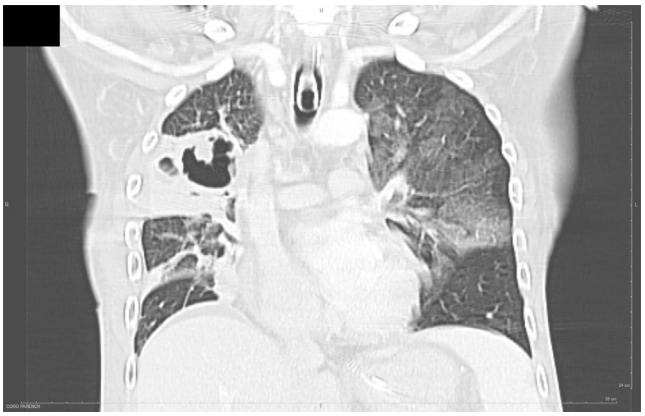

Fig. 1. Thoracic CT-scan showing a necrotizing pneumonia with abscess of the upper right lobe.
Scanner thoracique retrouvant une pneumopathie nécrosante abcédée du lobe supérieur droit.

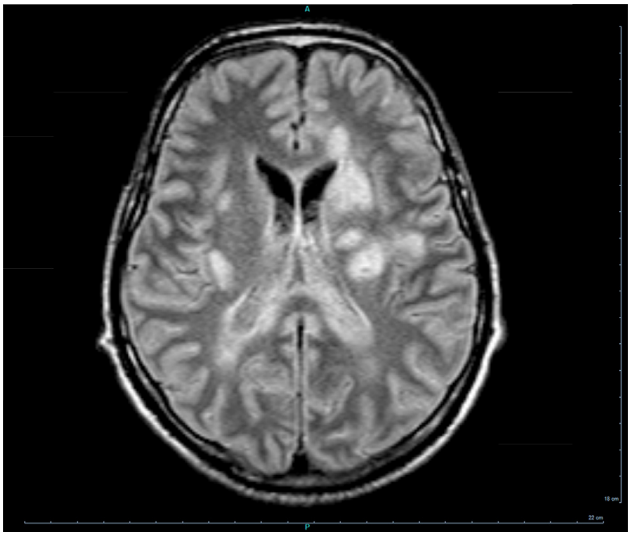

Fig. 2. Cerebral MRI showing multiple diffuse and bilateral brain abscesses (seven on this section).
IRM cérébrale montrant de multiples abcès cérébraux bilatéraux (sept sur cette seule coupe).

*ent*B, *mrk*D, *iut*A, *kfu*, and *ybt*S genes. The isolate belonged to sequence type 380 (ST380) as determined by multilocus sequence typing (MLST) [2]. All positive bacterial analyses found the same Kp with wild resistance phenotype.

After 68 days of intensive care complicated by multiple atelectasis, tracheotomy, pleural drainage failure with necessity of thoracotomy complicated by hemorrhagic shock, and a *Pseudomonas aeruginosa* ventilator-associated pneumonia, the patient did not recover his prior awareness state (Glasgow Coma Scale: score 3) nor spontaneous ventilation. We thus decided to limit active therapeutics and the patient died thereafter.

3. Discussion

Kp is a Gram-negative Enterobacteriaceae bacterium responsible for various infections. HvKp has been emerging since the middle of the eighties as a potentially responsible agent for severe and disseminated community-acquired infections, including among young and immunocompetent individuals [3,4]. The main infections due to classical phenotype Kp (cKp) include various sites (abdomen, urinary tract, blood, and lung) [5]. The emergence in the previous decades of hvKp strains leading to the most severe infections is a public health concern. The incidence may be underestimated owing to a non-systematic search for hypervirulent strains, unawareness of this clinical presentation out of Asia, and to the absence of a clear definition of a hypervirulent strain as it varies by studies. An objective diagnostic test is lacking [4], although the majority of hvKp are of K1 (mucoviscosity-associated gene A [*magA* gene]) or K2 serotype associated with the acquisition of a virulence plasmid with two important virulence genes (*rmpA* and/or *iutA)* [4,6]. A particular clinical phenotype related to community-acquired pyogenic liver abscesses (PLA), that may be associated with meningitis, endophtalmitis, and bacteremia, is mainly associated with the K1 serotype and sequence type (ST) 23 [3], especially among South-East Asia populations [5,6]. Among K2 serotype, several ST such as ST380, ST86, or ST375 are emerging in severe community-acquired infections [3]. The potential risk factors for this type of infection are Asian origin and diabetes [4,6]. The case fatality of infections due to HvKp is high, up to 42% according to some studies, and sequelae among survivors are frequent [4]. However, the case fatality varies by studies and case definitions used for hvKp. In Kp PLA, the case fatality is < 10% and seems to increase with the metastatic spread of the infection [6]. The first stage of this infection would be the colonization of the digestive tract mainly followed by infection through the endogenous route [4]. The infection might then develop transmucosally and then hematogenously via the portal system to reach general circulation [4]. The colonization of the oropharyngeal flora may also be an entry for low respiratory tract infections via microinhalations [4]. In the present case, the first septic localization remains unclear, as pulmonary or digestive route with secondary metastatic spread are plausible. Considering patient evolution, no digestive endoscopy was performed.

In vitro, hvKp strains are more resistant to the complement and to the bactericidal activity mediated by neutrophils [7]. There is currently no clear definition or test allowing for a simple and reproducible identification of hvKp strain, and the diagnosis is usually retained based on multiple arguments such as a severe clinical phenotype, the hypermucoviscous nature of the strain (string test > 5 mm), the serotype, and the presence of virulence genes. Serotypes K1 and K2 predominate among these hvKp strains [5,8], but some hypermucoviscous strains may also be non-K1-K2 [8]. Serotype K2 has a strong correlation with the resistance to intracellular lysis by the complement [6]. Nevertheless, the presence of serotype K1 or K2 is not sufficient to predict the virulence of the strain [4]. Other major virulence factors are the presence of genes that are responsible for the hypermucoviscous phenotype (*rmp*A) and iron-acquisition factors (aerobactin [*iutA* gene] and salmochelin) [4,6], usually located on a large virulence plasmid [4]. Multilocus sequencing has allowed for the identification of several strains associated with hypervirulence, such as ST23, ST57 (K1 serotype), ST86, ST375, and ST380

(emerging in K2 serotype) [2,4]. Multiplex PCR techniques have recently been developed to detect some hvKp strains [1].

The management of these infections is based on the drainage of abscesses as well as on an antibiotic therapy adapted to the infectious site and the resistance phenotype [6]. Third-generation cephalosporins are the treatment of choice for this type of infection [6]. Duration of the antibiotic treatment may vary, depending on the infectious site, size, and evolution of abscesses, and on the metastatic nature of the infection [6]. A minimum treatment duration of two weeks is usually considered [6]. A strict glycemic control proved effective in a study [9]. It should be noted that, although very rare, relapse occurring more than one year after the end of treatment has been described [4].

An increase in cKp resistance [5], that is also emerging in hvKp with the emergence of carbapenem-resistant strains, may be observed [10]. The recent emergence of antibiotic-resistant hvKp may complicate the treatment of these infections [10].

4. Conclusion

The community-acquired status, the severe and metastatic evolution of this infection, and the virulence profile guided the diagnosis of hvKp [4]. This case patient illustrates the severe and metastatic nature of this type of infection, with seven septic localizations and a fatal outcome, despite drainage and adapted antibiotic therapy in an immunocompetent host. It also highlights its extension out of Asia.

Contributors

M. Hentzien contributed to writing the article and took care of the literature review.

J. Rosman contributed to writing the article and was involved in the patient's care.

K. Brenkle was involved in the patient's care.

L. Mendes-Martins contributed to analyzing the hvKp strain in the laboratory of bacteriology.

D. Decre contributed to analyzing the hvKp strain in the laboratory of bacteriology and to writing the article.

P. Mateu contributed to writing and coordinating the article and was involved in the patient's care.

All authors read and approved the final version of the article.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Compain F, Babosan A, Brisse S, Genel N, Audo J, Ailloud F, et al. Multiplex PCR for detection of seven virulence factors and K1/K2 capsular serotypes of Klebsiella pneumoniae. J Clin Microbiol 2014;52:4377–80.

[2] Brisse S, Fevre C, Passet V, Issenhuth-Jeanjean S, Tournebize R, Diancourt L, et al. Virulent clones of Klebsiella pneumoniae: identification and evolutionary scenario based on genomic and phenotypic characterization. PloS One 2009;4:e4982.

[3] Decré D, Verdet C, Emirian A, Le Gourrierec T, Petit J-C, Offenstadt G, et al. Emerging severe and fatal infections due to Klebsiella pneumoniae in two university hospitals in France. J Clin Microbiol 2011;49:3012–4.

[4] Shon AS, Bajwa RPS, Russo TA. Hypervirulent (hypermucoviscous) Klebsiella pneumoniae: a new and dangerous breed. Virulence 2013;4:107–18.

[5] Keynan Y, Rubinstein E. The changing face of Klebsiella pneumoniae infections in the community. Int J Antimicrob Agents 2007;30:385–9.

[6] Siu LK, Yeh K-M, Lin J-C, Fung C-P, Chang F-Y. Klebsiella pneumoniae liver abscess: a new invasive syndrome. Lancet Infect Dis 2012;12:881–7.

[7] Pomakova DK, Hsiao C-B, Beanan JM, Olson R, MacDonald U, Keynan Y, et al. Clinical and phenotypic differences between classic and hypervirulent Klebsiella pneumonia: an emerging and under-recognized pathogenic variant. Eur J Clin Microbiol Infect Dis 2012;31:981–9.

[8] Yu VL, Hansen DS, Ko WC, Sagnimeni A, Klugman KP, von Gottberg A, et al. Virulence characteristics of Klebsiella and clinical manifestations of K. pneumoniae bloodstream infections. Emerg Infect Dis 2007;13:986–93.

[9] Lin J-C, Siu LK, Fung C-P, Tsou H-H, Wang J-J, Chen C-T, et al. Impaired phagocytosis of capsular serotypes K1 or K2 Klebsiella pneumoniae in type 2 diabetes mellitus patients with poor glycemic control. J Clin Endocrinol Metab 2006;91:3084–7.

[10] Yao B, Xiao X, Wang F, Zhou L, Zhang X, Zhang J. Clinical and molecular characteristics of multi-clone carbapenem-resistant hypervirulent (hypermucoviscous) Klebsiella pneumoniae isolates in a tertiary hospital in Beijing, China. Int J Infect Dis 2015;37:107–12.

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Lettres à la rédaction

Une tuberculose laryngée

Tracheotomy for laryngeal tuberculosis

Mots clés : Tuberculose laryngée ; Trachéotomie

Keywords: Laryngeal tuberculosis; Tracheotomy

1. Introduction

La tuberculose laryngée est une localisation rare de la tuberculose extra-pulmonaire. Le tableau clinique, le terrain ainsi que les lésions macroscopiques peuvent induire en erreur le clinicien en l'orientant vers une étiologie néoplasique. La tuberculose laryngée doit être évoquée devant des lésions inflammatoires chroniques ulcérées ou pseudo-tumorales, dès lors qu'une origine néoplasique a été exclue, y compris en l'absence de facteurs de risque de tuberculose ou d'images radiologiques pulmonaires associées. Nous rapportons le cas d'un homme de 32 ans ayant présenté une tuberculose laryngée ayant nécessité la réalisation d'une trachéotomie.

2. Présentation du cas

Un homme de 32 ans était hospitalisé pour une dyspnée d'apparition récente, dans un contexte de dysphonie plus ancienne. Dans ses antécédents, on notait un asthme traité par budésonide et formotérol à la demande et un tabagisme actif estimé à 15 paquets-année. Il était d'origine caucasienne et n'avait jamais quitté l'Europe occidentale. Il vivait dans de bonnes conditions sociales. Il avait été vacciné dans l'enfance par le BCG. Il présentait depuis environ 6 mois une dysphonie intermittente progressive sans dyspnée, ni fièvre ou altération de l'état général. Aucune investigation à visée diagnostique n'avait été réalisée avant son hospitalisation. Devant la persistance des signes et l'apparition récente d'une dyspnée au moindre effort, une laryngoscopie indirecte était réalisée retrouvant une lésion sténosante d'allure tumorale de l'endo-larynx avec immobilité de l'aryténoïde droite et une importante diminution de la motricité de l'aryténoïde gauche. Une corticothérapie par prednisolone 1 mg/kg par jour était débutée mais devant la majoration des symptômes une trachéotomie avait dû être réalisée. Le scanner cervico-thoracique montrait un épaississement hétérogène des replis pharyngo-épiglottiques prédominant à gauche ainsi qu'une réduction de l'expansion du sinus piriforme gauche. Ce processus s'étendait à la partie basse de la loge hyo-thyro-épiglottique et à la partie postérieure du mur pharyngolaryngé. Il existait une lyse de la corticale postérieure du cricoïde et de la partie antérieure du cartilage thyroïde. Des adénopathies infra-centimétriques jugulo-carotidiennes bilatérales étaient présentes. À l'étage thoracique, il était retrouvé des foyers alvéolaires multiples, confluents, réalisant des éléments pseudo-nodulaires du segment dorsal du lobe supérieur droit et apical du culmen, également en projection du Fowler des deux côtés et du segment postéro-basal gauche. Le scanner abdomino-pelvien était sans particularité. Des biopsies étagées, réalisées lors de la pan-endoscopie et d'une fibroscopie bronchique, retrouvaient des lésions inflammatoires à prédominance lymphocytaire avec la présence de nombreux granulomes épithélio-gigantocellulaires sans nécrose caséeuse. La PCR mycobactérie et l'examen direct après coloration de Ziehl-Neelsen revenaient positifs à *Mycobacterium tuberculosis* sur l'aspiration trachéale. Les sérologies VIH, hépatite B et C étaient négatives. Un traitement antituberculeux était initié selon le schéma standard par quadrithérapie. L'évolution était rapidement favorable avec une régression des lésions et une amélioration clinique, permettant notamment l'ablation de la trachéotomie après 10 jours de traitement, et une récupération complète de la phonation. L'enquête autour du patient n'a pas permis de trouver de sujets porteurs.

3. Discussion

La tuberculose laryngée constituait une présentation classique de la maladie avant l'apparition des traitements antibiotiques. Elle fait désormais partie des formes extra-pulmonaires les plus rares avec moins de 1 % de l'ensemble des cas de tuberculose [1]. Les cordes vocales restent la localisation la plus courante, suivie par le cartilage aryténoïde, les fausses cordes vocales et l'épiglotte [2,3]. Cette atteinte serait imputable soit à l'aérosolisation du germe dans le cadre d'une atteinte pulmonaire associée, soit à une possible dissémination hématogène et lymphatique [4]. Le tabac est un facteur prédisposant de par l'irritation chronique occasionnée de la muqueuse laryngée altérant les mécanismes de défense antimicrobienne [4]. Près de la moitié des patients atteints de tuberculose laryngée sont des fumeurs [1]. La tuberculose laryngée n'est généralement pas associée à une immunodépression sous-jacente. La laryngite tuberculeuse est suspectée devant une dysphonie avec raucité de la voix ainsi qu'une dysphagie haute chronique. Ces symptômes sont généralement précédés d'une toux. La dyspnée,

rare, témoigne d'un stade avancé [1,3,5]. La tomodensitométrie met en évidence des lésions diffuses, bilatérales, sans destruction de l'architecture laryngée. L'amputation du bord libre de l'épiglotte, parfois présent, oriente vers le diagnostic de tuberculose [3]. La laryngoscopie montre des lésions ulcéreuses ou tumorales, papillomateuses. Cet aspect peut évoquer un cancer du larynx d'autant plus que le terrain est le même. Les prélèvements biopsiques peuvent être pris en défaut et doivent être répétés [3]. Le traitement est celui d'une tuberculose classique permettant l'amendement rapide des symptômes en quelques semaines, et des lésions en quelques mois [1,4].

Le recours à la chirurgie est exceptionnel et concerne surtout les séquelles à type de fibrose laryngée, principale atteinte fonctionnelle au décours [3,5]. La trachéotomie peut être nécessaire dans de rares cas d'obstruction des voies aériennes [3].

4. Conclusion

Les formes laryngées de tuberculose sont rares mais doivent être évoquées devant des lésions ulcérées ou pseudo-tumorales non néoplasiques. Une atteinte pulmonaire doit systématiquement être recherchée. L'excellent pronostic fonctionnel sous traitement médical classique rend essentiel le diagnostic rapide, afin d'éviter le recours à des procédures thérapeutiques invasives telles que la chirurgie à la phase aiguë ou chronique séquellaire.

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Références

[1] Kurokawa M, Nibu K, Ichimura K, Nishino H. Laryngeal tuberculosis: a report of 17 cases. Auris Nasus Larynx 2015;42:305–10.
[2] Cruz S, Ribeiro A, Trigueiros N, Rodrigues e Rodrigues M. Laryngeal tuberculosis: a diagnosis not to be overlooked. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:325–6.
[3] El Ayoubi F, Chariba I, El Ayoubi A, Chariba S, Essakalli L. Primary tuberculosis of the larynx. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:361–4.
[4] Benwill JL, Sarria JC. Laryngeal tuberculosis in the United States of America: a forgotten disease. Scand J Infect Dis 2014;46:241–9.
[5] Wang C, Lin C, Wang C, Liu S, Jiang R. Laryngeal tuberculosis: a review of 26 cases. Otolaryngol Head Neck Surg 2007;137:582–8.

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L'efficacité de l'association tigécycline–colistine dans le traitement d'une méningite à *Acinetobacter baumannii* multi-résistant

The efficacy of the tigecycline–colistin association in the treatment of multi-resistant Acinetobacter baumannii meningitis

Mots clés : Tigécycline ; *Acinetobacter baumannii* ; Méningite ; Nosocomial

Keywords: Tigecycline; *Acinetobacter baumannii*; Meningitis; Nosocomial

1. Introduction

Les infections à *Acinetobacter baumannii* multirésistant sont de plus en plus fréquentes. Ces infections menacent l'arsenal thérapeutique vu l'émergence de résistance aux différents antibiotiques [1]. La tigécycline est un antibiotique récent actif sur ce type de germe multirésistant [2]. Cependant, l'efficacité de cet antibiotique en cas de méningite à ce germe n'est pas encore approuvée. Nous rapportons un cas de méningite à *A. baumannii* multirésistant traitée par une association d'antibiotique incluant la tigécycline.

2. Observation

Il s'agissait d'un patient âgé de 18 ans sans antécédents pathologiques particuliers admis en réanimation pour un traumatisme crânien grave suite un accident de la voie publique. L'examen initial montrait un patient en coma d'emblée avec un score de Glasgow à 3/15. Le reste de l'examen était sans particularités. Le patient a été intubé ventilé sédaté devant son problème neurologique. Un scanner cérébral montrait des foyers de contusions frontales gauches et un hématome au niveau du cervelet avec une dilatation quadri ventriculaire. Le patient a été opéré en urgence. Il a bénéficié d'une craniotomie par un volet frontal gauche avec une contusectomie frontale gauche. Par ailleurs, une dérivation ventriculaire externe a été mise en place. Cinq jours après, le patient présentait une fièvre en plateau à 40 °C, une réactivité en extension à la stimulation douloureuse. Par

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contre, il était stable sur le plan hémodynamique et respiratoire. Le scanner cérébral de contrôle ne montrait pas d'aggravation. L'aspect du liquide céphalorachidien drainé à travers la dérivation ventriculaire externe est devenu jaunâtre. À la biologie, on notait une hyperleucocytose à 32 000 éléments par millimètre cube avec une procalcitonine à 3,8 ng/ml. Un prélèvement du LCR a été réalisé. L'examen direct montrait un liquide trouble, 250 leucocytes à prédominance polynucléaires neutrophiles. L'examen biochimique montrait une hypoglycorrachie 0,55 mmol/L pour une glycémie à 5,2 mmol/L, une hyperprotéinorrachie 1,2 g/L. Le patient a été mis empiriquement sous imipenème et vancomycine et colistine. Après 48 heures, la culture s'est révélée positive à *A. baumannii.* Le lendemain, on a déterminé la sensibilité aux antibiotiques par diffusion du disque, et les concentrations minimales inhibitrices (CMI) par Etest. L'*A. baumannii* était sensible uniquement à la colistine (CMI = 0,094 mg/L) et à la tigécycline (CMI = 2 mg/L). Des prélèvements de LCR ont été réalisés quotidiennement et ont isolé le même germe trois jours de suite. Par contre, les hémocultures étaient négatives. Le patient a été mis sous tigécycline à dose de 100 mg, puis 50 mg toutes les 12 heures en intraveineux en association avec la colistine en intraveineux et intrathécal. Après 48 heures de cette association, le patient est devenu apyrétique et le prélèvement de LCR est devenu stérile. Le traitement était poursuivi pendant 21 jours avec une bonne tolérance et la dérivation a été retirée après 15 jours. Le patient était mis sortant après deux mois de séjour en réanimation avec un handicap sévère.

3. Discussion

Cette observation montre que la tigécycline associée à la colistine peut être efficace pour le traitement des méningites nosocomiales à *A. baumannii* multirésistant.

L'*A. baumannii* a émergé dans le monde entier pendant ces dernières années comme l'un des principaux agents responsable d'infection nosocomiale. Les pneumopathies nosocomiales est l'infection la plus fréquente par ce germe. Cependant, des bactériémies, des infections urinaires, des infections des parties molles et enfin des méningites sont de plus en plus décrites [1]. Les méningites à *A. baumannii* sont rares mais graves. Les principaux facteurs de risques sont les patients fragiles de réanimation, l'âge avancé, les dérivations ventriculaires externes et de façon générale toutes interventions neurochirurgicales [3]. L'imipenème a été pendant longtemps considéré comme le « Gold standard » dans le traitement des infections à *A. baumannii* [1]. Cependant, depuis quelques années, une émergence de germes multi-résistants à tous les antibiotiques utilisés en thérapeutique humaine a laissé considérer ce germe comme l'un des organismes qui menacent l'arsenal thérapeutique actuel [1].

La tigécycline est un antibiotique récent, dérivé semi-synthétique de la minocycline, appartenant à la classe des glycyclines [2]. Son spectre antibactérien englobe principalement *Staphylococcus aureus* résistant à la méticilline, les entérocoques résistants à la vancomycine, pneumocoque de sensibilité diminuée à la pénicilline, les bacilles à Gram négatif secrétants de bêtalactamase à spectre élargi (BLSE) dont l'*A. baumannii* [2].

Cependant, l'utilisation de la tigécycline dans les infections du système nerveux central n'est pas bien étudiée. Il y a peu de cas décrits concernant l'utilisation de la tigécycline pour le traitement des méningites à *A. baumannii* multi-résistant [3]. L'association de tigécycline à la colistine dans notre cas rapporté était le traitement de dernier recours devant ce germe qui était sensible uniquement à ces deux antibiotiques et après échec du traitement par colistine seule connue être active et efficace contre *A. baumannii* multi-résistant [3].

Le succès thérapeutique de notre cas est dû à plusieurs raisons. D'abord, l'association entre colistine et tigécycline, qui a montré une efficacité dans le traitement de différentes infections à *A. baumannii* multirésistant [1], semble être prometteuse pour le traitement des infections neuroméningées à ce germe [4]. La prescription de cette association est basée sur le mode d'action propre à chacune de ces deux molécules. En effet, la tigécycline agit en inhibant la synthèse protéique. En contrepartie, la colistine agit en détruisant les membranes cellulaires aboutissant à la lyse bactérienne. Ainsi, la fragilisation de la paroi bactérienne pourrait faciliter l'action de la tigécycline [4]. Ensuite, bien que la diffusion de la tigécycline dans le liquide céphalorachidien ne soit pas bonne [5], nous pensons que cet antibiotique peut atteindre un niveau acceptable en cas d'inflammation des méninges. En fait, peu de cas rapportés ayant étudié les concentrations de la tigécycline dans le liquide céphalorachidien [6]. Un tel dosage pourrait apporter des informations sur la diffusion et distribution de ces antibiotiques dans les méninges. D'autre part, certains préconisent l'administration de la tigécycline par voie intrathécale comme une autre option thérapeutique [7]. Les doses thérapeutiques de la tigécycline dans les cas rapportés de méningite nosocomiale sont identiques à notre conduite [5]. L'évolution favorable montre la pertinence de cette dose dans ce genre d'infection.

4. Conclusion

Les méningites à *A. baumannii* multirésistant sont graves compliquant le plus souvent les interventions neurochirurgicales. Le traitement de ces infections est un défi pour le clinicien et l'expérience thérapeutique face à ces germes mulitrésistants est limitée. La tigécycline peut avoir une place importante dans le traitement de ces infections. D'autres recherches seront nécessaires pour déterminer la place de cette molécule dans ces infections.

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Les auteurs déclarent ne pas avoir de liens d'intérêts.

Participation des auteurs

Kais Regaieg, Mabrouk Bahloul, Mounir Bouaziz : collection des données, interprétation des données et rédaction de l'article.

Olfa Turki, Basma Mnif : collection des données.

Références

[1] Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Infect Dis 2008;46(Suppl. 8):1254–63.
[2] Stahl JP. Tigecycline: a new antibiotic in ongoing clinical development. Med Mal Infect 2005;35(2):62–7.
[3] Rodriguez GA, Blanco A, Asensi V, Perez F, Rial JC, Pintado V, et al. Multidrugresistant *Acinetobacter meningitis* in neurosurgical patients with intraventricular catheters: assessment of different treatments. J Antimicrob Chemother 2008;61(Suppl. 4):908–13.
[4] Shrestha GS, Tamang S, Paneru HR, Shrestha PS, Keyal N, Acharya SP, et al. Colistin and tigecycline for management of external ventricular device-related ventriculitis due to multidrug-resistant *Acinetobacter baumannii*. J Neurosci Rural Pract 2016;7(3):450–2 [doi: 10.4103/0976-3147.176194].
[5] Wadi JA, Abu Al Rub M. Multidrug resistant *Acinetobacter* nosocomial meningitis treated successfully with parenteral tigecycline. Ann Saudi Med 2007;27:456–8.
[6] Ray L, Levasseur K, Nicolau DP, Scheetz MH. Cerebral spinal fluid penetration of tigecycline in a patient with *Acinetobacter baumannii* cerebritis. Ann Pharmacother 2010;44:582–6.
[7] Lauretti L, D'Alessandris QG, Fantoni M, D'Inzeo T, Fernandez E, Pallini R, et al. First reported case of intraventricular tigecycline for meningitis from extremely drug-resistant *Acinetobacter baumannii*. J Neurosurg 2016:1–4.

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Mots clés : Arthrite réactionnelle ; *Chlamydia trachomatis* ; Lymphogranulomatose vénérienne

Keywords: Reactive arthritis; *Chlamydia trachomatis*; Lymphogranuloma venereum

1. Introduction

L'arthrite réactionnelle (AR) est une arthropathie inflammatoire appartenant à la famille des spondyloarthrites. Elle survient généralement après une infection bactérienne de la sphère urogénitale ou digestive. Les génovars D à K de *Chlamydia trachomatis*, responsables chaque année dans le monde de 100 millions de cas d'infections sexuellement transmissibles (IST) [1], sont les agents étiologiques les plus courants d'AR. Depuis 2003, la lymphogranulomatose vénérienne (LGV), infection liée à *C. trachomatis* génovar L1 à L3, est à l'origine d'une épidémie d'ano-rectites touchant les hommes ayant des relations sexuelles avec des hommes (HSH) en Europe, en Amérique du Nord et en Australie [2]. Nous rapportons le deuxième cas d'AR secondaire à une LGV rectale en France [3].

2. Cas clinique

Un homme de 47 ans se présentait aux urgences de notre centre en novembre 2015 pour une douleur du membre inférieur gauche évoluant depuis huit jours.

Dans ses antécédents, on notait une infection par le VIH connue depuis 1990 (contamination sexuelle) et traitée par atazanavir, ritonavir, abacavir et lamivudine, un diabète de type 2 traité par metformine et glibenclamide. Six mois plus tôt, il avait présenté un tableau de rectite conduisant à la découverte concomitante d'une LGV, d'une gonococcie rectale et d'une syphilis latente précoce. Un traitement par benzathine benzylpénicilline, ceftriaxone (injections intramusculaires uniques) et doxycycline pendant 21 jours avaient permis la disparition des symptômes.

Huit jours avant l'admission aux urgences, il avait consulté son infectiologue devant la récidive d'une rectite. Le tableau digestif était apparu dix jours auparavant. La pratique récente d'un lavement dans un sauna était notée. La recherche de *C. trachomatis* par PCR sur un écouvillon rectal et l'introduction d'une antibiothérapie probabiliste par doxycycline (200 mg par jour) étaient prescrites. Des douleurs de rythme inflammatoire de toute la jambe gauche étaient ensuite apparues.

À l'admission aux urgences, le patient était apyrétique et présentait un épanchement du genou gauche associé à un œdème inflammatoire de jambe. L'échographie-doppler veineux des membres inférieurs éliminait une phlébite. Le bilan biologique objectivait un syndrome inflammatoire (CRP à 94 mg/L). Un érysipèle était évoqué et un traitement par pristinamycine était débuté. Quatre jours plus tard, face à une persistance des symptômes, une échographie articulaire réalisée en consultation de rhumatologie objectivait une arthrite talonaviculaire et une ténosynovite du court fibulaire gauches. La ponction du genou gauche retirait 10 mL de liquide citrin dont la formule cytologique était inflammatoire avec 2900 éléments par mm^3 (20 % de polynucléaires neutrophiles, 80 % de lymphocytes). Il n'y avait pas de bactérie à l'examen direct et en culture, pas de cristaux. La PCR Chlamydia trachomatis (PCR CT) sur écouvillon rectal (réalisée en consultation d'infectiologie) revenait positive et le typage par PCR temps réel retrouvait un génovar L2b, confirmant une LGV rectale. La recherche de *C. trachomatis* par biologie moléculaire sur liquide articulaire était également positive mais le typage moléculaire est resté sans succès en raison d'un inoculum bactérien très faible. La recherche de gonocoque était négative. Le traitement par infiltration intra-articulaire d'hydrocortisone et anti-inflammatoires non stéroïdiens par voie orale, associé à la poursuite de la doxycycline pour un total de

[1] Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Infect Dis 2008;46(Suppl. 8):1254–63.
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[4] Shrestha GS, Tamang S, Paneru HR, Shrestha PS, Keyal N, Acharya SP, et al. Colistin and tigecycline for management of external ventricular device-related ventriculitis due to multidrug-resistant *Acinetobacter baumannii*. J Neurosci Rural Pract 2016;7(3):450–2 [doi: 10.4103/0976-3147.176194].
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21 jours permettait une disparition rapide de l'oligoarthrite. La recherche du HLA-B27 était négative et l'imagerie par résonance magnétique (IRM) des sacro-iliaques était normale. Le diagnostic d'AR associée à une LGV rectale était retenu. Aucune récidive articulaire n'est survenue après dix mois de suivi.

3. Discussion

Notre patient a présenté une oligoarthrite 10 à 15 jours après l'apparition d'une rectite en rapport avec une LGV. Le tableau oligoarticulaire asymétrique associé à une ténosynovite, l'infection à *C. trachomatis* de survenue récente, la détection d'ADN de *C. trachomatis* dans le liquide synovial, la résolution du tableau articulaire sous traitement anti-inflammatoire sont autant d'arguments forts permettant de conclure au diagnostic d'AR à *C. trachomatis* génovar L2b. L'infection à *Chlamydia* comme facteur déclenchant du syndrome de Reiter et de l'AR est connu depuis de nombreuses années. Il est estimé que 4 à 8 % des patients ayant eu une infection urogénitale à *C. trachomatis* sont susceptibles de développer une AR [4]. Le mécanisme supposé est celui d'une dissémination par voie systémique vers la cavité articulaire dans laquelle la bactérie persiste sous une forme aberrante et non cultivable.

L'épidémie de LGV rectale détectée chez les HSH depuis 2003 est associée au génovariant L2b, décrit pour la première fois en 2005 [5]. Le nombre de LGV en Angleterre et en France depuis 2003 excède 4000 et 2000 cas déclarés respectivement [6,7]. Depuis cette période, huit cas seulement (dont le cas présenté ici) d'AR associée à *C. trachomatis* génovar L2b ont été rapportés, cette association semble donc rare. Les patients étaient infectés par le VIH dans sept cas. Un cas concernait une femme. Notre cas se distingue par la présence d'ADN de *C. trachomatis* dans le liquide synovial rendant l'association entre l'épisode de LGV et la survenue de l'arthrite peu équivoque. L'évolution des cas décrits était systématiquement favorable avec une résolution du tableau articulaire sans récidive sous traitement antibiotique par doxycycline 200 mg par jour pendant trois semaines associé à un traitement anti-inflammatoire systémique par corticoïdes ou AINS.

4. Conclusions

C. trachomatis génovar L2b, à l'origine de l'épidémie de LGV rectale dans la population des HSH, est susceptible de déclencher un tableau d'AR. La survenue d'une mono/oligoarthrite chez un HSH ayant présenté récemment une rectite doit faire évoquer ce diagnostic. L'incidence de la LGV augmentant chaque année en France et en Europe, cette complication mérite d'être connue.

Participation des auteurs

AD a rédigé le cas clinique.

NMC et CC ont pris en charge le patient et participé à la rédaction du cas clinique.

OP et AT ont réalisé les analyses microbiologiques et aidé à la rédaction du cas clinique.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

Références

[1] Rowley J, Toskin I, Ndowa F, World Health Organization (Reproductive Health Research) [consulté le 6 octobre 2016] http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf.

[2] de Vrieze NHN, de Vries HJC. Lymphogranuloma venereum among men who have sex with men. An epidemiological and clinical review. Expert Rev Anti Infect Ther 2014;12(6):697–704.

[3] El Karoui K, Mechai F, Ribadeau-Dumas F, Viard J-P, Lecuit M, de Barbeyrac B, et al. Reactive arthritis associated with L2b lymphogranuloma venereum proctitis. Sex Transm Infect 2009;85(3):180–1.

[4] Zeidler H, Hudson AP. New insights into *Chlamydia* and arthritis. Promise of a cure? Ann Rheum Dis 2014;73(4):637–44.

[5] Spaargaren J, Fennema HSA, Morré SA, de Vries HJC, Coutinho RA. New lymphogranuloma venereum *Chlamydia trachomatis* variant, Amsterdam. Emerg Infect Dis 2005;11(7):1090–2.

[6] de Barbeyrac B, Bébéar C, Laurier-Nadalié C, Peuchant O, Touati A. Dix ans de surveillance de la lymphogranulomatose vénérienne (LGV) ano-rectale et des ano-rectites à souche non-L de Chlamydia trachomatis (CT) en France 2004-2014 [Internet]; 2015. Disponible sur : http://www.cnrchlamydiae.u-bordeaux2.fr/wp-content/uploads/2015/05/Bilan-Réseau-LGV-Année-20142.pdf [cité 11 juin 2016].

[7] Childs T, Simms I, Alexander S, Eastick K, Hughes G, Field N. Rapid increase in lymphogranuloma venereum in men who have sex with men, United Kingdom, 2003 to September 2015. Euro Surveill 2015;20(48), http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30076 [pii=30076].

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